# EAST Search History

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| S1 | 0 | lamotrigene same particle adj size | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 07:32 |
| S2 | 7 | lamotrigene | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:24 |
| S3 | 23310 | particles same specific adj surface adj area | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:04 |
| S4 | 163 | S3 and pharmaceutical adj composition | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:51 |
| S5 | 0 | lamotrigene same Teva adj Pharmaceutical? | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:54 |
| S6 | 0 | lamotrigene same Teva | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:52 |
| S7 | 1 | ("3090693").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/23 18:21 |
| S8 | 1 | ("5861179").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/23 18:21 |
| S9 | 0 | bet near particle adj size near surface adj area | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 07:33 |
| S10 | 1134 | particle adj size near surface adj area | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 07:43 |
| S11 | 3 | S10 and BET adj measure? | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 12:25 |
| S12 | 3 | (("4847249") or ("5942510") or ("5861179")).PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 12:31 |
| S13 | 1 | ("4602017").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 15:06 |

# EAST Search History

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| S14 | 1 | ("0021121").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 15:08 |
| S15 | 1 | ("4486354").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 15:08 |
| S16 | 7 | (("4486354") or ("5643591") or ("4602017") or ("6639072") or ("5925755") or ("5942510") or ("5861179")).PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/25 09:16 |
| S17 | 4552 | "424/489".CCLS. | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:20 |
| S18 | 3731 | S17 and @ad<="20030801" | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:07 |
| S19 | 160 | ((JUDITH) near2 (ARONHIME)).INV. | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:49 |
| S20 | 5 | ((GUY) near2 (SAMBURSKI)).INV. | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:20 |
| S21 | 88 | ((JUDITH) near2 (ARONHIME)).INV. | EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:21 |
| S22 | 6 | ((GUY) near2 (SAMBURSKI)).INV. | EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:21 |
| S23 | 697 | "514/242".CCLS. | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:21 |
| S24 | 509 | S23 and @ad<="20030801" | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:22 |
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| S26 | 8 | "LAMOTRIGENE" | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:29 |
| S27 | 0 | "6-(2,3-dichlorophenyl)-1,2, 4-triazine-3,5-diamine" | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:44 |
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| S33 | 65 | lamotrigine.ti. | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 16:07 |
| S34 | 202 | lamotrigine.clm. | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 16:07 |
| S35 | 12 | S33 and @ad<="20030801" | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:14 |
| S36 | 91 | S34 and @ad<="20030801" | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:08 |
| S37 | 0 | ("5861179").URPN. | USPAT | OR | ON | 2007/04/04 16:09 |
| S38 | 1 | ("5912345").URPN. | USPAT | OR | ON | 2007/04/04 16:10 |
| S39 | 38 | S36 and particl?? | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:15 |

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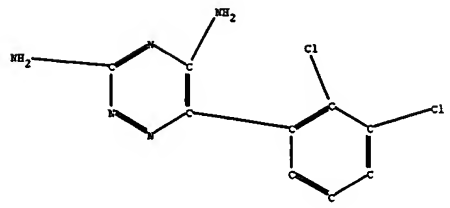
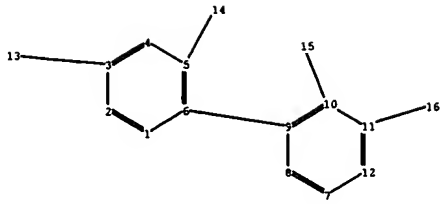
STN
lwl
4/4/07





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13 14 15 16
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
3-13 5-14 6-9 10-15 11-16
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
3-13 5-14
exact bonds :
6-9 10-15 11-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS

10/511987 LAMOTRIGINE reg no-text search USPGPUB search

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=> d his

     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

     FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1              STRUCTURE UPLOADED
L2            3 S L1 SSS SAM
L3          128 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4           25 S L3/P
                E US20050238724/PN,PRN,AN
L5            0 S E3/RN
L6            1 S E3

     FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7            0 S L6

     FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
                E LAMOTRIGINE+ALL/CT
                S LAMOTRIGINE/CN

     FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8            1 S LAMOTRIGINE/CN

     FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9         1265 S L8
L10          27 S "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

     FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
L11           1 S 84057-84-1/RN

     FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007
L12        1265 S L11
L13      111187 S L10 OR L12  AND PARTICLE OR GRANULE
L14           0 S L12 (N) PARTICLE
L15           0 S L12 (W) PARTICLE
L16          46 S L12 AND CNS
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10/511987 LAMOTRIGINE reg no-text search USPGPUB search

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L1 STRUCTURE UPLOADED

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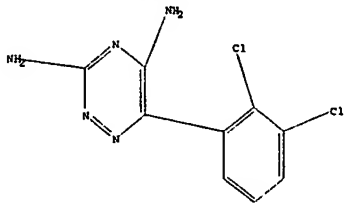
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss sam
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SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 9 TO 360
PROJECTED ANSWERS: 3 TO 163

L2 3 SEA SSS SAM L1

=> d l2 1-3 ibib abs
'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
FIDE - All substance data, except sequence data
IDE - FIDE, but only 50 names
SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD - Protein sequence data, includes RN



4/4/07

10/511987 LAMOTRIGINE reg no-text search USPGPUB search

SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

CALC - Table of calculated properties
EPROP - Table of experimental properties
PROP - EPROP and CALC

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

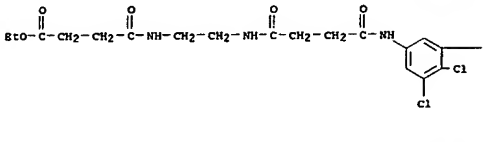
HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):ide

L2 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 885316-75-6 REGISTRY
ED Entered STN: 23 May 2006
CN Butanoic acid, 4-[[2-[[4-[[3,4-dichloro-5-(3,5-diamino-1,2,4-triazin-6-yl)phenyl]amino]-1,4-dioxobutyl]amino]ethyl]amino]-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)
MF C21 H26 Cl2 N8 O5
SR CA
LC STN Files: CA, CAPLUS



10/511987 LAMOTRIGINE reg no-text search USPGPUB search

PAGE 1-A



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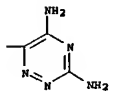
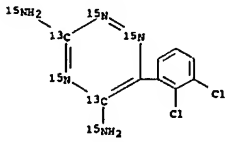


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 478189-71-8 REGISTRY
ED Entered STN: 06 Jan 2003
CN 1,2,4-Triazine-3,5-diamine-3,5-13C2-N,N',1,2,4-15N5, 6-(2,3-dichlorophenyl)- (9CI) (CA INDEX NAME)
MF C9 H7 Cl2 N5
SR CA
LC STN Files: CA, CAPLUS, CASREACT



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 454695-04-6 REGISTRY
ED Entered STN: 25 Sep 2002
CN Formamide, N,N-dimethyl-, compd. with 6-(2,3-dichlorophenyl)-1,2,4-



10/511987 LAMOTRIGINE reg no-text search USPGPUB search

triazine-3,5-diamine (3:2) (9CI) (CA INDEX NAME)
MF C9 H7 Cl2 N5 . 3/2 C3 H7 N O
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

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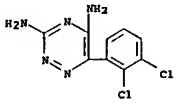
CRN 84057-84-1
CMF C9 H7 Cl2 N5



CM 2

CRN 68-12-2
CMF C3 H7 N O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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FULL SCREEN SEARCH COMPLETED - 212 TO ITERATE

100.0% PROCESSED 212 ITERATIONS 128 ANSWERS
SEARCH TIME: 00.00.01

L3 128 SEA SSS FUL L1

=> fil hcaplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 178.40 178.61

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 4 Apr 2007 VOL 146 ISS 15
FILE LAST UPDATED: 3 Apr 2007 (20070403/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his

(FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1 STRUCTURE UPLOADED
L2 3 S L1 SSS SAM
L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007

=> a l3/p
L4 25 L3/P

=> d l4 1-25 ibib abs

L4 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:411970 HCAPLUS
DOCUMENT NUMBER: 144:425648
TITLE: Lamotrigine analogs for production of anti-lamotrigine antibodies and use as immunoassay reagents
INVENTOR(S): Ouyang, Anlong; Arabshahi, Lili; Roberts, Mark; Wall, Melissa
PATENT ASSIGNEE(S): Seradyn, Inc., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006047372 | A2 | 20060504 | WO 2005-US38100 | 20051021 |
| WO 2006047372 | A3 | 20060727 | | |
| WO 2006047372 | A9 | 20061005 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW





RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| US 2006115865 | A1 | 20060601 | US 2005-254650 | 20051020 |
| PRIORITY APPLN. INFO.: | | | US 2004-621764P | P 20041025 |
| | | | US 2005-254650 | A 20051020 |

OTHER SOURCE(S): MARPAT 144:425648
AB The invention discloses a lamotrigine analogs that have substituents at the triazine 3-position and on the benzene 4-position and 5-position. The lamotrigine analogs can include immunogenic moieties that can be used to prepare anti-lamotrigine antibodies, or antigenic moieties that can be used in immunodiagnostic assays for lamotrigine. Also, the lamotrigine analog can include tracer moieties for detecting the presence or amount of the analog during an immunodiagnostic assay. Addnl., the lamotrigine analogs can be used in immunodiagnostic assays to compete with lamotrigine for binding with anti-lamotrigine antibodies. Lamotrigine analog preparation is described.

L4 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:411913 HCAPLUS
DOCUMENT NUMBER: 144:425647
TITLE: Immunoassays for lamotrigine
INVENTOR(S): Ouyang, Anlong; Arabshahi, Lili; Roberts, Mark; Wall, Melissa
PATENT ASSIGNEE(S): Seradyn, Inc., USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006047451 | A2 | 20060504 | WO 2005-US38258 | 20051021 |

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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| US 2006172356 | A1 | 20060803 | US 2005-254637 | 20051020 |
| PRIORITY APPLN. INFO.: | | | US 2004-621764P | P 20041025 |
| | | | US 2005-254637 | A 20051020 |

OTHER SOURCE(S): MARPAT 144:425647
AB Generally, the present invention relates to lamotrigine analogs that have substituents at the triazine 3-position and on the benzene 4-position and 5-position. The lamotrigine analogs can include immunogenic moieties that can be used to prepare anti-lamotrigine antibodies, or antigenic moieties that can be used in immunodiagnostic assays for lamotrigine. Also, the lamotrigine analog can include tracer moieties for detecting the presence





or amount of the analog during an immunodiagnostic assay. Addnl., the lamotrigine analogs can be used in immunodiagnostic assays to compete with lamotrigine for binding with anti-lamotrigine antibodies.

L4 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1010006 HCAPLUS
DOCUMENT NUMBER: 144:312050
TITLE: A new approach to the synthesis of lamotrigine and other 3,5-diamino-1,2,4-triazine derivatives
AUTHOR(S): Ulomskii, E. N.; Shestakova, T. S.; Deev, S. L.; Rusinov, V. L.; Chupakhin, O. N.
CORPORATE SOURCE: Ural State Technical University, Yekaterinburg, 620002, Russia
SOURCE: Russian Chemical Bulletin (2005), 54(3), 726-732
CODEN: RCBUBY; ISSN: 1066-5285
PUBLISHER: Springer Science+Business Media, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new in principle method for the synthesis of 6-aryl(hetaryl)-3,5-diamino-1,2,4-triazines by decomposition of pre-synthesized tetrazolo[1,5-b][1,2,4]triazines was developed. The advantages of this method over traditional methods were demonstrated using the synthesis of a modern antiepileptic preparation lamotrigine, as an example. The crystal structure of 6-phenyltetrazolo[1,5-b][1,2,4]triazin-7-amine is presented [monoclinic, space group P21/c, a 10.935(2), b 6.7330(10), c 13.279(3) Å, β 93.20(3)°, V 976.1(3) Å3, Z 4].
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:421792 HCAPLUS
DOCUMENT NUMBER: 142:430313
TITLE: Process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (Lamotrigine) via reaction of 2,3-dichlorobenzoyl chloride with cuprous cyanide and then with aminoguanidine bicarbonate followed by cyclization.
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): Torrent Pharmaceuticals Ltd., India
SOURCE: Indian, 12 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,





CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

| | | | | |
|---|---|---|---|---|
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |
| US 6111101 | A | 20000829 | US 1999-456501 | 19991208 |
| | | | IN 1998-CA2171 | A 19981214 |
| PRIORITY APPLN. INFO.: | | | WO 1999-IB1955 | W 19991207 |

OTHER SOURCE(S): CASREACT 142:430313
AB Lamotrigine was prepared by reaction of 2,3-dichlorobenzoyl chloride with CuCN (1:1-2 molar ratio) in MeCN and a coaolvent to produce dichlorobenzoyl cyanide, reaction of the latter with aminoguanidine bicarbonate to produce the cyanoimine intermediate 2-[cyano(2,3-dichlorophenyl)methylene]hydrazinecarboximidamide, and cyclization of this in the presence of aqueous KOH at 80°-reflux.

L4 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:421470 HCAPLUS
DOCUMENT NUMBER: 141:7119
TITLE: Preparation of crystalline lamotrigine and its monohydrate
INVENTOR(S): Manjunatha, Sulur G.; Kulkarni, Ashok Krishna; Kishore, Charugundla; Bokka, Ravisankar
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: Brit. UK Pat. Appl., 25 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| GB 2395483 | A | 20040526 | GB 2003-15608 | 20030703 |
| WO 2005003104 | A2 | 20050113 | WO 2004-IN186 | 20040628 |
| WO 2005003104 | A3 | 20050922 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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| PRIORITY APPLN. INFO.: | | | GB 2003-15608 | A 20030703 |
| OTHER SOURCE(S): | | | CASREACT 141:7119 | |

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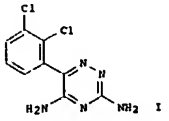

I

AB The invention relates to crystalline lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) (I) monohydrate and anhydrous lamotrigine. An improved process for manufacturing these products comprises reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in aqueous mineral acid, optionally together with a water miscible organic solvent, at 30-80° to produce the 2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (Schiff base) (II). The Schiff base II is further cyclized in aqueous organic solvent, e.g. alc. to produce pure lamotrigine of a pharmaceutically acceptable quality which on further drying at 45-50° under vacuum yields lamotrigine monohydrate, and/or on further drying at 100-110° yields anhydrous lamotrigine. The lamotrigine monohydrate or anhydrous lamotrigine thereby produced may then be brought into association with a pharmaceutically acceptable carrier for administration to a patient in need thereof.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:390214 HCAPLUS
DOCUMENT NUMBER: 140:391299
TITLE: Process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Dalmases Barjoan, Pere; Beasa Bellmunt, Jordi
PATENT ASSIGNEE(S): Laboratorios Vita, S.A., Spain
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004039767 | A1 | 20040513 | WO 2003-IB4763 | 20031027 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| ES 2209639 | A1 | 20040616 | ES 2002-2502 | 20021031 |





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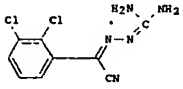
|---|---|---|---|---|
| ES 2209639 | B1 | 20050801 | | |
| AU 2003272019 | A1 | 20040525 | AU 2003-272019 | 20031027 |
| EP 1556361 | A1 | 20050727 | EP 2003-753860 | 20031027 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2006052625 | A1 | 20060309 | US 2005-532397 | 20050422 |
| US 7179913 | B2 | 20070220 | | |
| NO 2005002574 | A | 20050527 | NO 2005-2574 | 20050527 |
| PRIORITY APPLN. INFO.: | | | ES 2002-2502 A | 20021031 |
| | | | WO 2003-IB4763 W | 20031027 |

OTHER SOURCE(S): CASREACT 140:391299
GI



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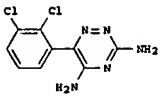


II

AB A method for preparing the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile (I; m.p. 180-183°) which comprises the condensation reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a non-aqueous medium in the presence of methanesulfonic acid, which produces good I yields and short reaction times. I is cyclized into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (II; m.p. 217°) under reflux in an aliph alc. (e.g., ethanol) or alc.-water mixture
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:267313 HCAPLUS
DOCUMENT NUMBER: 140:303705
TITLE: Two-step process for the synthesis of high-purity 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine from 2,3-dichlorobenzoyl cyanide and aminoguanidine dimesylate





INVENTOR(S): Neu, Jozsef; Gizur, Tibor; Toerley, Jozsef; Csabai, Janos; Vegh, Ferenc; Kalvin, Peter; Tarkanyi, Gabor
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004026845 | A1 | 20040401 | WO 2003-HU72 | 20030918 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| HU 200203114 | A2 | 20040528 | HU 2002-3114 | 20020920 |
| CA 2498761 | A1 | 20040401 | CA 2003-2498761 | 20030918 |
| AU 2003267676 | A1 | 20040408 | AU 2003-267676 | 20030918 |
| EP 1539720 | A1 | 20050615 | EP 2003-748368 | 20030918 |
| EP 1539720 | B1 | 20061122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| AT 346051 | T | 20061215 | AT 2003-748368 | 20030918 |
| IN 2005KN00267 | A | 20060714 | IN 2005-KN267 | 20050224 |
| US 2006178511 | A1 | 20060810 | US 2005-528379 | 20051129 |
| PRIORITY APPLN. INFO.: | | | HU 2002-3114 A | 20020920 |
| | | | WO 2003-HU72 W | 20030918 |

OTHER SOURCE(S): CASREACT 140:303705
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB High-purity 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I; i.e., lamotrigine) is prepared by the condensation reaction of 2,3-dichlorobenzoyl cyanide (II) with 1-2 mol equivalent of an aminoguanidine salt (e.g., aminoguanidine dimesylate) in 3-6 mol equivalent of methanesulfonic acid, then the obtained adduct (III) is transformed without isolation into the desired product by contacting it with magnesium oxide, followed by crystallization of the product from an appropriate organic solvent (e.g., acetone).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:507707 HCAPLUS
DOCUMENT NUMBER: 139:69292
TITLE: Process for the preparation of lamotrigine and related 3,5-diamino-6-substituted-1,2,4-triazines via





cyclization of cyanoiminoguanidines.
INVENTOR(S): Guntoori, Bhaskar Reddy; Che, Daqing; Murthy, K. S. Keshava
PATENT ASSIGNEE(S): Brantford Chemicals Inc., Can.
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6586593 | B1 | 20030701 | US 2002-46383 | 20020116 |
| CA 2366521 | A1 | 20030624 | CA 2001-2366521 | 20011224 |
| CA 2366521 | C | 20070306 | | |
| WO 2003078407 | A1 | 20030925 | WO 2002-CA1926 | 20021218 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002367765 | A1 | 20030929 | AU 2002-367765 | 20021218 |
| EP 1458692 | A1 | 20040922 | EP 2002-807048 | 20021218 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| NZ 533734 | A | 20051223 | NZ 2002-533734 | 20021218 |
| PRIORITY APPLN. INFO.: | | | CA 2001-2366521 A | 20011224 |
| | | | WO 2002-CA1926 W | 20021218 |

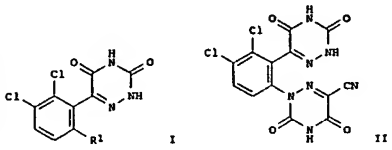
OTHER SOURCE(S): CASREACT 139:69292; MARPAT 139:69292
GI



I

AB Title compds. [I; R = (substituted) alkyl, aryl], were prepared by reaction of RCOCN with aminoguanidine in the presence of an organic sulfonic acid in an organic solvent under anhydrous conditions to give (HO)C(R)(CN)NHNC(NH2)2, dehydration of this to give NCC(R){:NH:C(NH2)2}, and cyclization of the latter. Thus, aminoguanidine hydrochloride in DMF was treated with MeSO3H and 2,3-dichlorobenzoyl chloride followed by stirring for 1 h, addition of SOCl2, and stirring for 1 h to give 39.2% iminoguanidine derivative The latter was refluxed with KOH in Me2CHOH to give 82% lamotrigine monohydrate.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:365795 HCAPLUS
DOCUMENT NUMBER: 140:199296
TITLE: Synthesis of oxo analogs of Lamotrigine and related compounds
AUTHOR(S): Hlavac, Jan; Buchtik, Roman; Slouka, Jan; Hradil, Pavel; Wiedermannova, Iveta
CORPORATE SOURCE: Department of Organic Chemistry, Palacky University, Olomouc, CZ-771 46, Czech Rep.
SOURCE: ARKIVOC (Gainesville, FL, United States) (2003), (1), 22-28
CODEN: AGFUAR
URL: http://www.arkat-usa.org/ark/journal/2003/General/2-556P/556P.pdf
PUBLISHER: Arkat USA Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:199296
GI



I II

AB Lamotrigine oxo analogs I (R1 = H, Cl, Br, iodo, HO) were prepared from azauracil I (R1 = NH2) via the formation of the intermediate diazonium salt. Coupling of this diazonium salt with Et cyanoacetylcarbamate gave the corresponding carbamoyl hydrazone, which underwent intramol. cyclization upon reflux in pyridine to afford bis(triazinyl)benzene II containing two 6-azauracil rings.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:334829 HCAPLUS
DOCUMENT NUMBER: 138:343889
TITLE: Novel pharmaceutical compounds containing drugs bound to polypeptides
INVENTOR(S): Picariello, Thomas
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 4662 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 24
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|





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|---|---|---|---|---|
| WO 2003034980 | A2 | 20030501 | WO 2001-US43089 | 20011114 |
| WO 2003034980 | A8 | 20051103 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2428971 | A1 | 20030501 | CA 2001-2428971 | 20011114 |
| EP 1401374 | A1 | 20040331 | EP 2001-274606 | 20011114 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2006516948 | T | 20060713 | JP 2003-537549 | 20011114 |
| US 2004063628 | A1 | 20040401 | US 2002-156527 | 20020529 |
| US 7060708 | B2 | 20060613 | | |
| US 2007060500 | A1 | 20070315 | US 2006-392878 | 20060330 |
| PRIORITY APPLN. INFO.: | | | US 2000-274622P | P 20001114 |
| | | | US 1999-265415 | B2 19990310 |
| | | | US 1999-411238 | B2 19991004 |
| | | | WO 2000-US5693 | A 20000306 |
| | | | US 2000-642820 | A2 20000822 |
| | | | US 2000-247594P | P 20001114 |
| | | | US 2000-247622P | P 20001114 |
| | | | US 2000-247684P | P 20001114 |
| | | | US 2000-248528P | P 20001116 |
| | | | US 2000-248620P | P 20001116 |
| | | | US 2000-248659P | P 20001116 |
| | | | US 2000-248660P | P 20001116 |
| | | | US 2000-248662P | P 20001116 |
| | | | US 2000-248663P | P 20001116 |
| | | | US 2000-248685P | P 20001116 |
| | | | US 2000-248733P | P 20001116 |
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| | | | US 2000-248738P | P 20001116 |
| | | | US 2000-248748P | P 20001116 |
| | | | US 2000-248764P | P 20001116 |
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| | | | US 2000-248769P | P 20001116 |
| | | | US 2000-248770P | P 20001116 |
| | | | US 2000-248771P | P 20001116 |
| | | | US 2000-248772P | P 20001116 |
| | | | US 2000-248774P | P 20001116 |
| | | | US 2000-248776P | P 20001116 |
| | | | US 2000-248777P | P 20001116 |
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| | | | US 2000-248779P | P 20001116 |
| | | | US 2000-248782P | P 20001116 |
| | | | US 2000-248787P | P 20001116 |
| | | | US 2000-248794P | P 20001116 |
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| | | | US 2000-248796P | P 20001116 |
| | | | US 2000-248797P | P 20001116 |
| | | | US 2001-933708 | A2 20010822 |





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|---|---|---|---|---|
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| | | | US 2001-987458 | B2 20011114 |
| | | | WO 2001-US43089 | W 20011114 |
| | | | US 2001-988034 | B2 20011116 |
| | | | US 2001-988071 | B2 20011116 |
| | | | WO 2001-US43115 | B2 20011116 |
| | | | WO 2001-US43117 | B2 20011116 |
| | | | US 2002-356381P | P 20020222 |
| | | | US 2002-366258P | P 20020322 |
| | | | US 2002-156527 | A2 20020529 |
| | | | US 2003-507012P | P 20030930 |
| | | | US 2004-567800P | P 20040505 |
| | | | US 2004-567802P | P 20040505 |
| | | | US 2004-568011P | P 20040505 |
| | | | US 2004-923088 | A2 20040823 |
| | | | WO 2004-US32131 | A2 20040930 |

AB Compns. comprising polypeptides and drugs covalently attached to the polypeptide are disclosed. Also provided is a method for delivery of these drugs to a patient comprising administering to the patient a composition comprising a polypeptide and a drug covalently attached to the polypeptide. Also provided is a method for protecting drugs from degradation comprising covalently attaching them to a polypeptide. Also provided is a method for controlling release of drugs from a composition comprising covalently attaching them to the polypeptide.

L4 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:76761 HCAPLUS
DOCUMENT NUMBER: 138:137336
TITLE: Method for producing lamotrigine from alpha-oxo-2,3-dichlorophenylacetamidinoaminoguanidino hydrazone by ring closure reaction
INVENTOR(S): Schneider, Geza; Gegoe, Csaba Lehel; Ondi, Levente; Mate, Attila Gergely; Lukacs, Ferenc; Nyerges, Miklos; Garaczi, Sandor
PATENT ASSIGNEE(S): Helm AG, Germany; CP Pharma Gyogyszergyarto Kft.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003008393 | A1 | 20030130 | WO 2002-EP7433 | 20020704 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10134980 | A1 | 20030213 | DE 2001-10134980 | 20010717 |
| DE 10134980 | C2 | 20030528 | | |
| EP 1311492 | A1 | 20030521 | EP 2002-758308 | 20020704 |
| EP 1311492 | B1 | 20040908 | | |





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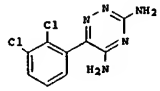
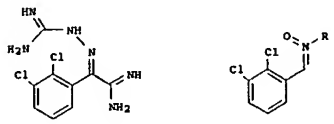
|---|---|---|---|---|
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE | | | | |
| CA 2417435 | C | 20040113 | CA 2002-2417435 | 20020704 |
| CA 2417435 | A1 | 20030130 | | |
| ES 2224074 | T3 | 20050301 | ES 2002-2758308 | 20020704 |
| US 2003191310 | A1 | 20031009 | US 2003-343225 | 20030515 |
| US 6683182 | B2 | 20040127 | | |
| PRIORITY APPLN. INFO.: | | | DE 2001-10134980 | A 20010717 |
| | | | WO 2002-EP7433 | W 20020704 |

OTHER SOURCE(S): CASREACT 138:137336; MARPAT 138:137336
GI



I

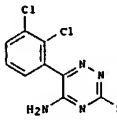


II III

AB The invention relates to a method for producing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine (I)), or its pharmaceutically acceptable salts, by ring closure reaction from α-oxo-2,3-dichlorophenylacetamidinoaminoguanidino hydrazone (II) or its salts. The preparation of II from N-oxides, III (R = linear, branched or cyclic (un)substituted alkyl, aryl, aralkyl), or their salts, are also described. Thus, I was prepared from 2,3-Cl2C6H3CH:N(O)Ph, via cyanation with NaCN, amination to the acetamidine hydrochloride, reaction with aminoguanine bicarbonate to give II·HCl, treatment with aqueous NaOH to give the free base, which is cyclized to I; cyclization of II·HCl gives I·HCl.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:549382 HCAPLUS
DOCUMENT NUMBER: 138:24695
TITLE: Synthesis of stable isotopically labelled versions of Lamotrigine and its methylated metabolite
AUTHOR(S): Manning, Calvin O.; Wadsworth, Alan H.; Fellows, Ian

CORPORATE SOURCE: Chemical Development, GlaxoSmithKline Research and Development, Stevenage, SG1 2NY, UK
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (2002), 45(7), 611-618
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:24695
GI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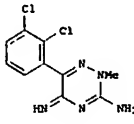

II

AB Lamotrigine (I) is a sodium channel antagonist used for the treatment of epilepsy. Stable isotopically labeled [M + 7] analogs of I and of its N-methylated metabolite II were prepared using [M + 5] labeled [13C, 15N4]-aminoguanidine, obtained from labeled thiourea. The overall yield for isotopically labeled II was 34% from [M + 3] labeled [13C, 15N2]-thiourea.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

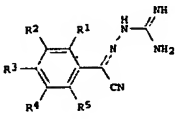
L4 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:631908 HCAPLUS
DOCUMENT NUMBER: 135:195578
TITLE: Process for preparing substituted benzoyl cyanide amidinohydrazones as intermediates for synthesis of 3,5-diamino-6-phenyl-1,2,4-triazines
INVENTOR(S): Nadaka, Vladimir; Lexner, Jael; Kaspi, Joseph
PATENT ASSIGNEE(S): Chemagis Ltd., Israel
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

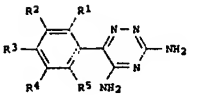
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1127873 | A2 | 20010829 | EP 2001-103660 | 20010223 |
| EP 1127873 | A3 | 20030507 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| IL 134730 | A | 20031031 | IL 2000-134730 | 20000225 |
| CA 2337280 | A1 | 20010825 | CA 2001-2337280 | 20010215 |
| HU 200100740 | A2 | 20011128 | HU 2001-740 | 20010215 |
| US 2001025118 | A1 | 20010927 | US 2001-789634 | 20010222 |
| US 6329521 | B2 | 20011211 | | |

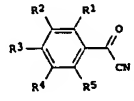




PRIORITY APPLN. INFO.: IL 2000-134730 A 20000225
OTHER SOURCE(S): CASREACT 135:195578; MARPAT 135:195578
GI


I


II


III

AB The title compds. [I; R1-R5 = H, halo, alkyl, etc.], useful as intermediates for synthesis of 1,2,4-triazines II (active in the treatment of CNS disorders), were prepared by reacting the benzoyl cyanides III with aminoguanidine bicarbonate in a mixture of a water-soluble solvent and polyphosphoric acid. Thus, reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in the presence of polyphosphoric acid in MeCN afforded 2,3-dichlorobenzoyl cyanide amidinohydrazone which was then heated under reflux in PrOH to give 2,3-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

L4 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:507682 HCAPLUS
DOCUMENT NUMBER: 135:108912
TITLE: Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (lamotrigine)
INVENTOR(S): Radhakrishnan, Tarur Venkatasubramanian; Sasikumar, Thoovara Mohan; Srivastava, Anita Ranjan
PATENT ASSIGNEE(S): RPG Life Sciences Limited, India
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001049669 | A1 | 20010712 | WO 2000-IN1 | 20000103 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, | | | | |





SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| GB 2372988 | A | 20020911 | GB 2002-14791 | 20000103 |
| GB 2372988 | B | 20040407 | | |
| BR 2000016980 | A | 20021001 | BR 2000-16980 | 20000103 |
| DE 10085384 | T0 | 20021212 | DE 2000-10085384 | 20000103 |
| DE 10085384 | B4 | 20060614 | | |
| AU 763244 | B2 | 20030717 | AU 2000-44288 | 20000103 |
| IN 2002MN00829 | A | 20040313 | IN 2002-MN829 | 20020619 |
| US 6639072 | B1 | 20031028 | US 2002-149429 | 20020624 |

PRIORITY APPLN. INFO.: WO 2000-IN1 A 20000103
AB The title compound was prepared by hydrogenation of 2,3-Cl2C6H3NO2 in MeOH at 80 psi H pressure using Raney Ni catalyst at 30° to give 2,3-Cl2C6H3NH2 which was diazotized and converted to nitrile with CuCN/NaCN at 65-70°. The resulting 2,3-Cl2C6H3CN was hydrolyzed to give 2,3-Cl2C6H3CO2 which was converted to acid chloride at 80° with SOCl2. The 2,3-Cl2C6H3COCl was cyano-dehalogenated with CuCN/KI by refluxing in PhCl under an inert atmospheric and the product 2,3-Cl2C6H3COCN was condensed with aminoguanidine bicarbonate in PhMe in the presence of H2SO4 and p-MeC6H4SO3H at 100-120°, followed by in-situ cyclization of the Schiff base by refluxing with MeONa in MeOH. Crude lamotrigine is purified by recrystn. from MeOH.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:369058 HCAPLUS
DOCUMENT NUMBER: 136:14957
TITLE: Isolation of lamotrigine 2-N-glucuronide from guinea pig urine
AUTHOR(S): Yeh, Shih-Wcei; Yu, Hsiu-Ying
CORPORATE SOURCE: School of Pharmacy, National Taiwan University, Taipei, 100, Taiwan
SOURCE: Chinese Pharmaceutical Journal (Taipei, Taiwan) (2000), 52(5), 241-249
CODEN: CPHJEP; ISSN: 1016-1015
PUBLISHER: Pharmaceutical Society of Republic of China
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lamotrigine (LT) is a novel anticonvulsant. Its major metabolite in human is 2-N-glucuronide (LT-2NG). In order to investigate the metabolic characteristics of LT in our laboratory, a reference standard of LT-2NG was required.
The purpose of this experiment was to isolate pure LT-2NG from the urine of LT-treated guinea pigs. The pooled urine of guinea pigs fed with LT was eluted with methanol through XAD-2 column. LT-2NG in the eluent was purified by semi-preparative HPLC equipped with a C8 column and a UV detector set at 267 nm. The mobile phase for HPLC was 0.01M ammonium acetate (pH 6.6) containing 12% of methanol. The isolated LT-2NG was confirmed by mass, 1H NMR and 13C NMR spectroscopic anal. The mol. ion 432.1, a downfield anomeric proton at 5.39 ppm, and an upfield shift (-6.9 ppm) of the triazine ring C-3 indicate attachment of the glucuronide to the N-2 of LT. These spectra were identical with the reported spectra of LT-2NG isolated from human urine.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT





L4 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:421116 HCAPLUS
DOCUMENT NUMBER: 133:60362
TITLE: An improved process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |

PRIORITY APPLN. INFO.: IN 1998-CA2171 A 19981214
WO 1999-IB1955 W 19991207
AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) (I) useful as antiepileptic drug (no data) is prepared in a 3 step process. Thus, 2,3-dichlorobenzoylchloride was treated with cuprous cyanide in presence of acetonitrile and a solvent to produce 2,3-dichlorobenzoyl cyanide, further with aminoguanidine and cyclized to produce I.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:795469 HCAPLUS
DOCUMENT NUMBER: 132:26963
TITLE: Preparation of 1,2,4-triazine derivative, and its use as reference marker for testing purity and stability of lamotrigine
INVENTOR(S): Edmeades, Lorraine Mary; Griffith-Skinner, Nigel Arthur; Hill, Derek Anthony; Hill, Graham Thornton; Packham, Terrence William
PATENT ASSIGNEE(S): The Wellcome Foundation Limited, UK
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 963980 | A2 | 19991215 | EP 1999-200695 | 19990310 |
| EP 963980 | A3 | 20000531 | | |
| EP 963980 | B1 | 20020605 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| SG 85628 | A1 | 20020115 | SG 1999-1252 | 19990325 |
| MX 9902202 | A | 20000831 | MX 1999-2202 | 19990305 |
| KR 2000005611 | A | 20000125 | KR 1999-7632 | 19990309 |
| HR 990074 | A1 | 20001031 | HR 1999-74 | 19990309 |
| ZA 9901951 | A | 19990816 | ZA 1999-1951 | 19990310 |
| JP 2989189 | B2 | 19991213 | JP 1999-63792 | 19990310 |
| JP 2000009714 | A | 20000114 | | |
| NO 9901151 | A | 19991213 | NO 1999-1151 | 19990310 |
| CN 1238454 | A | 19991215 | CN 1999-103445 | 19990310 |
| AU 9920319 | A | 20000106 | AU 1999-20319 | 19990310 |
| TR 9900520 | A2 | 20000121 | TR 1999-520 | 19990310 |
| HU 9900592 | A2 | 20000428 | HU 1999-592 | 19990310 |
| BR 9900984 | A | 20000502 | BR 1999-984 | 19990310 |
| NZ 334590 | A | 20000728 | NZ 1999-334590 | 19990310 |
| CA 2265194 | C | 20001010 | CA 1999-2265194 | 19990310 |
| US 6333198 | B1 | 20011225 | US 1999-265670 | 19990310 |
| EP 1170588 | A1 | 20020109 | EP 2001-203376 | 19990310 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 218552 | T | 20020615 | AT 1999-200695 | 19990310 |
| PT 963980 | T | 20021031 | PT 1999-200695 | 19990310 |
| ES 2178342 | T3 | 20021216 | ES 1999-200695 | 19990310 |
| CN 1306210 | A | 20010801 | CN 2000-122208 | 20000725 |
| US 2002055177 | A1 | 20020509 | US 2001-940422 | 20010829 |
| NO 2003002753 | A | 19991213 | NO 2003-2753 | 20030617 |

PRIORITY APPLN. INFO.: GB 1998-12413 A 19980610; EP 1999-200695 A3 19990310; US 1999-265670 A3 19990310

AB A method of testing the purity or stability to degradation of a sample of lamotrigine or a pharmaceutical dosage form comprising lamotrigine consists of assaying the sample for the presence of a compound selected from 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5-(4H)-one and N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide (I). A process for producing compound I, is also disclosed. Lamotrigine was treated with 2,3-dichlorobenzoyl chloride to give I. TLC-densitometry was used to determine I in lamotrigine tablets.

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:473716 HCAPLUS
DOCUMENT NUMBER: 127:81468
TITLE: Fluorophenyl-triazine and pyrimidine derivatives as compounds acting on the central nervous system
INVENTOR(S): Torrens Jover, Antoni; Frigola Constansa, Jordi
PATENT ASSIGNEE(S): Laboratorios Del Dr. Esteve, S.A., Spain; Torrens Jover, Antoni; Frigola Constansa, Jordi
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent



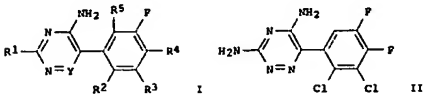


LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9720827 | A1 | 19970612 | WO 1996-EP5593 | 19961204 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| FR 2741879 | A1 | 19970606 | FR 1995-14354 | 19951205 |
| AU 9711943 | A | 19970627 | AU 1997-11943 | 19961204 |
| ES 2128960 | A1 | 19990516 | ES 1996-2667 | 19961205 |
| ES 2128960 | B1 | 20000116 | | |

PRIORITY APPLN. INFO.: FR 1995-14354 A 19951205; WO 1996-EP5593 W 19961204

OTHER SOURCE(S): CASREACT 127:81468; MARPAT 127:81468
GI



AB Novel fluorophenyl-triazine and pyrimidine derivs. I and their physiol. acceptable salts are disclosed [wherein R1 = amino, 1-piperazinyl or 4-alkylpiperazin-1-yl, where alkyl = C1-4 chain, preferably Me; R2, R3, R4 = halo, preferably F or Cl; R5 = H or halo, preferably F or Cl; Y = N, CH]. A method for preparing the compds. is also disclosed, as are pharmaceutical compns. containing a pharmaceutically acceptable carrier and at least one such compound The compds. are CNS agents which act by inhibiting the release of glutamate. Examples include 13 syntheses, 1 standard formulation, and biol. data for 5 compds. For instance, 2,3-dichloro-4,5-difluorobenzoic acid (prepared in 3 steps) was converted to the acid chloride (99%) and then to the acyl cyanide (98%), and the latter was condensed with aminoguanidine bicarbonate and cyclized (31%) to give title compound II. In a test for prevention of hypoxic death in mice, II had an ED50 of 0.6 mg/kg i.p., vs. 1.2 mg/kg for lamotrigine.

L4 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:548552 HCAPLUS
DOCUMENT NUMBER: 125:195694
TITLE: Preparation of lamotrigine.
INVENTOR(S): Winter, Raymond Geoffrey; Sawyer, David Alan; Germain, Andrew
PATENT ASSIGNEE(S): Wellcome Foundation Limited, UK
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2



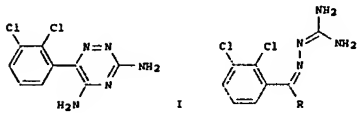


DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9620934 | A1 | 19960711 | WO 1995-GB3048 | 19951229 |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9643115 | A | 19960724 | AU 1996-43115 | 19951229 |
| EP 800520 | A1 | 19971015 | EP 1995-941817 | 19951229 |
| EP 800520 | B1 | 20020619 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV | | | | |
| HU 77346 | A2 | 19980330 | HU 1997-1867 | 19951229 |
| HU 224688 | B1 | 20051228 | | |
| JP 11501007 | T | 19990126 | JP 1995-520803 | 19951229 |
| RU 2145602 | C1 | 20000220 | RU 1997-112881 | 19951229 |
| AT 219487 | T | 20020715 | AT 1995-941817 | 19951229 |
| PT 800520 | T | 20021129 | PT 1995-941817 | 19951229 |
| ES 2177672 | T3 | 20021216 | ES 1995-941817 | 19951229 |
| FI 9702719 | A | 19970827 | FI 1997-2719 | 19970624 |
| US 5912345 | A | 19990615 | US 1997-836153 | 19970625 |

PRIORITY APPLN. INFO.: GB 1994-26439 A 19941230; GB 1994-26447 A 19941230; WO 1995-GB3048 W 19951229

OTHER SOURCE(S): CASREACT 125:195694; MARPAT 125:195694
GI



AB Lamotrigine (I) was prepared by irradiation of (II; R = CN, CONH2) with UV or visible radiation in an organic solvent, or, when R = CN, by heating. Thus, II (R = CN) was refluxed in 1-propanol under irradiation from a medium pressure Hg lamp for 8 h to give 73% lamotrigine.

L4 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:546365 HCAPLUS
DOCUMENT NUMBER: 125:195693
TITLE: Preparation of lamotrigine.
INVENTOR(S): Lee, Grahame Roy
PATENT ASSIGNEE(S): Wellcome Foundation Limited, UK
SOURCE: PCT Int. Appl., 25 pp.





CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9620935 | A1 | 19960711 | WO 1995-GB3049 | 19951229 |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9643116 | A | 19960724 | AU 1996-43116 | 19951229 |
| EP 800521 | A1 | 19971015 | EP 1995-941818 | 19951229 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV | | | | |
| HU 77347 | A2 | 19980330 | HU 1997-1875 | 19951229 |
| JP 11507011 | T | 19990622 | JP 1995-520618 | 19951229 |
| RU 2162081 | C2 | 20010120 | RU 1997-112921 | 19951229 |
| FI 9702720 | A | 19970827 | FI 1997-2720 | 19970624 |
| US 5925755 | A | 19990720 | US 1997-836152 | 19970625 |

PRIORITY APPLN. INFO.: GB 1994-26448 A 19941230; WO 1995-GB3049 W 19951229

AB Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I), is prepared by treating 6-(2,3-dichlorophenyl)-5-chloro-2-thiomethyl-1,2,4-triazine (II) with NH3. Thus, II (preparation given) was heated with ethanolic NH3 in a sealed tube at 180° and 280 psi for 72 h to give I.

L4 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:128970 HCAPLUS
DOCUMENT NUMBER: 116:128970
TITLE: Preparation of 6-aminophenyl-3,5-diamino-1,2,4-triazines as neuroprotective agents
INVENTOR(S): Leach, Michael John; Nobbs, Malcolm Stuart
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 459829 | A1 | 19911204 | EP 1991-304962 | 19910531 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| ZA 9104158 | A | 19930301 | ZA 1991-4158 | 19910530 |
| CA 2043642 | A1 | 19911202 | CA 1991-2043642 | 19910531 |
| FI 9102622 | A | 19911202 | FI 1991-2622 | 19910531 |
| AU 9178099 | A | 19911205 | AU 1991-78099 | 19910531 |
| AU 630811 | B2 | 19921105 | | |
| HU 60726 | A2 | 19921028 | HU 1991-1827 | 19910531 |
| JP 06025193 | A | 19940201 | JP 1991-235335 | 19910531 |

PRIORITY APPLN. INFO.: GB 1990-12312 A 19900601
OTHER SOURCE(S): MARPAT 116:128970

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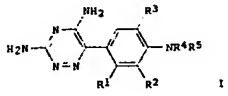

I

AB Title compds. (I; 1 of R1-R3 = Cl and the others = H or Cl; R4, R5 = H, alkyl) were prepared Thus, 2,5,3-Cl2(H2N)C6H2CO2H was converted in 3 steps to 2,3,5-Cl3C6H2COCN which was cyclocondensed with H2NC(:NH)NHNH2 and the product nitrated to give, after reduction, I (R1-R3 = Cl, R4 = R5 = H). The latter had IC50 of <10 μM against glutamate release from rat brain slices.

L4 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:112505 HCAPLUS
DOCUMENT NUMBER: 108:112505
TITLE: Preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate as an antiepileptic
INVENTOR(S): Sawyer, David Alan; Copp, Frederick Charles
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 247892 | A1 | 19871202 | EP 1987-304776 | 19870529 |
| EP 247892 | B1 | 19910424 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| DK 8702759 | A | 19871201 | DK 1987-2759 | 19870529 |
| DK 166278 | B | 19930329 | | |
| DK 166278 | C | 19930823 | | |
| FI 8702406 | A | 19871201 | FI 1987-2406 | 19870529 |
| FI 90770 | B | 19931215 | | |
| FI 90770 | C | 19940325 | | |
| AU 8773684 | A | 19871203 | AU 1987-73684 | 19870529 |
| AU 597982 | B2 | 19900614 | | |
| JP 62289570 | A | 19871216 | JP 1987-134772 | 19870529 |
| JP 07051571 | B | 19950605 | | |
| HU 45978 | A2 | 19880928 | HU 1987-2487 | 19870529 |
| HU 196769 | B | 19890130 | | |
| ZA 8703896 | A | 19890125 | ZA 1987-3896 | 19870529 |
| US 4847249 | A | 19890711 | US 1987-56136 | 19870529 |
| AT 62902 | T | 19910515 | AT 1987-304776 | 19870529 |
| CA 1286670 | C | 19910723 | CA 1987-538395 | 19870529 |
| IL 82710 | A | 19920115 | IL 1987-82710 | 19870529 |
| PRIORITY APPLN. INFO.: | | | GB 1986-13183 A | 19860530 |
| | | | EP 1987-304776 A | 19870529 |

AB The title compound (I.isethionate), useful as an anticonvulsant (no data),





was prepared by reaction of I with 2-hydroxyethanesulfonic acid (II) or by reaction of I salts with the anion of II. A 1.0 M solution of Na isethionate in H2O was passed through a column of IR 120 (H) ion exchange resin. I (preparation given) was added to the resulting II and the solution was filtered and evaporated Recrystn. from industrial methylated spirit gave 72% I.isethionate.

L4 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1985:542021 HCAPLUS
DOCUMENT NUMBER: 103:142021
TITLE: Triazine compounds having cardiovascular activity
INVENTOR(S): Allan, Geoffrey; Miller, Alastair Ainslie; Sawyer, David Alan
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 142306 | A2 | 19850522 | EP 1984-307374 | 19841026 |
| EP 142306 | A3 | 19861120 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| US 4649139 | A | 19870310 | US 1984-663682 | 19841022 |
| DK 8405121 | A | 19850428 | DK 1984-5121 | 19841026 |
| FI 8404212 | A | 19850428 | FI 1984-4212 | 19841026 |
| AU 8434758 | A | 19850509 | AU 1984-34758 | 19841026 |
| AU 564667 | B2 | 19870820 | | |
| JP 60109577 | A | 19850615 | JP 1984-225636 | 19841026 |
| DD 224033 | A5 | 19850626 | DD 1984-268757 | 19841026 |
| HU 36102 | A2 | 19850828 | HU 1984-4003 | 19841026 |
| HU 191566 | B | 19870330 | | |
| ES 537104 | A1 | 19860416 | ES 1984-537104 | 19841026 |
| ZA 8408388 | A | 19860625 | ZA 1984-8388 | 19841026 |
| SU 1371500 | A3 | 19880130 | SU 1984-3805251 | 19841026 |
| IL 73332 | A | 19880630 | IL 1984-73332 | 19841026 |
| PL 144899 | B1 | 19880730 | PL 1984-250213 | 19841026 |
| CA 1261328 | A1 | 19890926 | CA 1984-466473 | 19841026 |
| PRIORITY APPLN. INFO.: | | | GB 1983-28757 A | 19831027 |
| OTHER SOURCE(S): | MARPAT 103:142021 | | | |

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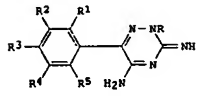

I

AB Tautomeric iminotriazinamines I [R = (un)substituted C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C3-10 cycloalkyl; R1-R5 = H, halogen, alkenyloxy, acyl, acyloxy, cyano, NO2, aryl, alkylthio, (un)substituted alkyl,





alkenyl, alkynyl, alkoxy, amino; R1R2, R2R3, R3R4, R4R5 = CH:CHCH:CH] were prepared Thus, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine was alkylated with Me2CHI to give I-HI (R = Me2CH, R1 = R2 = Cl; R3-R5 = H) which was converted to the mesylate salt (II) (12% overall yield). II at 1 mg/kg i.v. to rats increased the amount of aconitine required to elicit ventricular arrhythmias by 490% compared with 84% for 1 mg/kg verapamil.

L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:89397 HCAPLUS
DOCUMENT NUMBER: 98:89397
TITLE: Substituted aromatic compounds
INVENTOR(S): Baxter, Martin G.; Elphick, Albert R.; Miller, Alistair A.; Sawyer, David A.
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Can., 26 pp. Division of Can. Appl. No. 353,081.
CODEN: CAXXA4
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CA 1133938 | A2 | 19821019 | CA 1981-373126 | 19810316 |
| CA 1112643 | A1 | 19811117 | CA 1980-353081 | 19800530 |
| US 4486354 | A | 19841204 | US 1981-308805 | 19811005 |
| AU 566870 | B2 | 19871105 | AU 1983-14051 | 19830428 |
| US 4602017 | A | 19860722 | US 1984-583286 | 19840227 |
| FI 8400888 | A | 19840306 | FI 1984-888 | 19840306 |
| FI 73203 | B | 19870529 | | |
| FI 73203 | C | 19870910 | | |
| PRIORITY APPLN. INFO.: | | | GB 1979-19257 A | 19790601 |
| | | | CA 1980-353081 A3 | 19800530 |
| | | | US 1980-154198 A1 | 19800529 |
| | | | FI 1980-1758 A | 19800530 |
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| | | | US 1981-302365 A1 | 19810915 |

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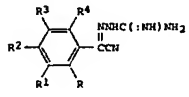

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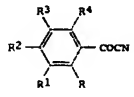
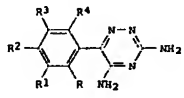


II



III





AB [(Cyanobenzylidene)amino]guanidines I (R-R4 = H, halo, alkyl, F3C; RR1 = HC:CHCH:CH, halobenzo, trifluoromethylbenzo, alkylbenzo) were prepared from the benzoyl cyanides II and H2NNHC(:NH)NH2 and were useful as intermediates in the preparation of anticonvulsant triazines III. Thus, 2,3-Cl2C6H3COCl was treated with CuCN to give 2,3-Cl2C6H3COCN which was treated with H2NNHC(:NH)NH2 to give I (R = R1 = Cl, R2 = R3 = R4 = H), which was cyclized by KOH to give III (R = R2 = Cl, R2 = R3 = R4 = H) (IV). The anticonvulsant ED50 of IV was 2.4 mg/kg in the maximal electroshock test.

L4 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1981:208914 HCAPLUS
DOCUMENT NUMBER: 94:208914
TITLE: 1,2,4-Triazine derivatives, pharmaceutical compositions and intermediates utilized for their preparation
INVENTOR(S): Baxter, Martin George; Elphick, Albert Reginald; Miller, Alistair Ainslie; Sawyer, David Alan
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 21121 | A1 | 19810107 | EP 1980-103032 | 19800530 |
| EP 21121 | B1 | 19830511 | | |
| R: BE, CH, DE, FR, GB, LU, NL, SE | | | | |
| DK 8002338 | A | 19801202 | DK 1980-2338 | 19800530 |
| DK 153787 | B | 19880905 | | |
| DK 153787 | C | 19890116 | | |
| FI 8001758 | A | 19801202 | FI 1980-1758 | 19800530 |
| FI 67844 | B | 19850228 | | |
| FI 67844 | C | 19850610 | | |
| AU 8058906 | A | 19801204 | AU 1980-58906 | 19800530 |
| AU 530999 | B2 | 19830804 | | |
| JP 56025169 | A | 19810310 | JP 1980-71580 | 19800530 |
| JP 01044706 | B | 19890929 | | |
| ES 491998 | A1 | 19810516 | ES 1980-491998 | 19800530 |
| DD 151309 | A5 | 19811014 | DD 1980-221474 | 19800530 |
| ZA 8003250 | A | 19810127 | ZA 1980-3250 | 19800530 |
| AT 8002896 | A | 19820715 | AT 1980-2896 | 19800530 |
| AT 370697 | B | 19830225 | | |
| EP 59987 | A1 | 19820915 | EP 1982-102293 | 19800530 |
| EP 59987 | B1 | 19850814 | | |
| R: BE, CH, DE, FR, GB, LU, NL, SE | | | | |
| PL 124029 | B1 | 19821231 | PL 1980-224633 | 19800530 |
| HU 24621 | A2 | 19830328 | HU 1980-1364 | 19800530 |
| HU 182086 | B | 19831228 | | |
| IL 60201 | A | 19840531 | IL 1980-60201 | 19800530 |
| CS 234018 | B2 | 19850314 | CS 1980-3829 | 19800530 |
| SU 1055331 | A3 | 19831115 | SU 1980-2932704 | 19800602 |
| US 4486354 | A | 19841204 | US 1981-308805 | 19811005 |
| US 4602017 | A | 19860722 | US 1984-583286 | 19840227 |
| FI 8400888 | A | 19840306 | FI 1984-888 | 19840306 |

| | | | | | |
|---|---|---|---|---|---|
| | FI 73203 | B | 19870529 | | |
| | FI 73203 | C | 19870910 | | |
| | JP 61033163 | A | 19860217 | JP 1985-121370 | 19850604 |
| | JP 01044179 | B | 19890926 | | |
| PRIORITY APPLN. INFO.: | | | | GB 1979-19257 | A 19790601 |
| | | | | US 1980-154198 | A1 19800529 |
| | | | | EP 1980-103032 | A 19800530 |
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| | | | | US 1981-302365 | A1 19810915 |

OTHER SOURCE(S): MARPAT 94:208914
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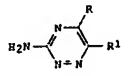

I

AB Triazines I (R = NH2, acylamino, aminomethyleneamino; R1 = substituted Ph) were prepared Thus, 2,3-Cl2C6H3I was Grignard carboxlated and the 2,3-Cl2C6H3CO2H converted to the chloride and treated with CuCN to give 2,3-Cl2C6H3COCN which was cyclized with aminoguanidine bicarbonate to I (R = NH2, R1 = 2,3-Cl2C6H3). The latter compound had an anticonvulsant ED50 of 2.4 mg/kg orally in mice.

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IC    ICM  A61K
CC    63-6 (Pharmaceuticals)
TI    Pharmaceutical composition containing lamotrigine particles of defined
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ST    lamotrigine particle morphol seizure treatment
IT    Phenols, biological studies
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IT    Alcohols, biological studies
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IT    Quaternary ammonium compounds, biological studies
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IT    Drug delivery systems
         (liqs., oral; pharmaceutical composition containing lamotrigine particles of
         defined morphol. and excipients)
IT    Drug delivery systems
         (particles; pharmaceutical composition containing lamotrigine particles of
         defined morphol. and excipients)
IT    Acacia
      Anticonvulsants
      Chondrules
      Egg yolk
      Human
      Seizures
         (pharmaceutical composition containing lamotrigine particles of defined
morphol.
         and excipients)
IT    Alcohols, biological studies
      Bentonite, biological studies
      Carbohydrates, biological studies
      Casein, biological studies
      Gelatins, biological studies
      Kaolin, biological studies
      Polyoxyalkylenes, biological studies
      Tocopherols
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (pharmaceutical composition containing lamotrigine particles of defined
morphol.
         and excipients)
IT    Drug delivery systems
         (solids, oral; pharmaceutical composition containing lamotrigine particles
of
         defined morphol. and excipients)
IT    Fats and Glyceridic oils, biological studies
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (vegetable, hydrogenated; pharmaceutical composition containing lamotrigine
         particles of defined morphol. and excipients)
IT    Fats and Glyceridic oils, biological studies
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (vegetable; pharmaceutical composition containing lamotrigine particles of
         defined morphol. and excipients)
IT    9003-01-4D, crosslinked
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         (Carbomer; pharmaceutical composition containing lamotrigine particles of
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IT    9003-39-8D, crosslinked
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
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         (Crospovidone; pharmaceutical composition containing lamotrigine particles
of
         defined morphol. and excipients)
IT    99-96-7D, alkyl esters
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         (Parabens; pharmaceutical composition containing lamotrigine particles of
         defined morphol. and excipients)
IT    7631-86-9, Colloidal silicon dioxide, biological studies
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (colloidal; pharmaceutical composition containing lamotrigine particles of
         defined morphol. and excipients)
IT    9004-34-6, Cellulose, biological studies
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (microcryst.; pharmaceutical composition containing lamotrigine particles of
         defined morphol. and excipients)
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      studies  128-44-9, Sodium saccharin  471-34-1, Calcium carbonate,
      biological studies  526-95-4, Gluconic acid  527-07-1, Sodium gluconate
      532-32-1, Sodium benzoate  546-93-0, Magnesium carbonate  994-36-5,
      Sodium citrate  1309-48-4, Magnesium oxide, biological studies
      1327-43-1, Magnesium aluminum silicate  7447-40-7, Potassium chloride,
      biological studies  7631-90-5, Sodium bisulfite  7647-14-5, Sodium
      chloride, biological studies  7681-57-4, Sodium metabisulfite
      7758-87-4, Tribasic calcium phosphate  7778-18-9, Calcium sulfate
      7789-77-7, Dibasic calcium phosphate dihydrate  8013-17-0, Invert sugar
      8027-56-3, Liquid glucose  9000-30-0, Guar gum  9000-65-1, Tragacanth
      9000-69-5, Pectin  9002-89-5, Polyvinyl alcohol  9003-39-8, Povidone
      9004-32-4, Carboxymethylcellulose sodium  9004-53-9, Dextrin  9004-57-3,
      Ethyl cellulose  9004-62-0, Hydroxyethyl cellulose  9004-64-2,
      Hydroxypropyl cellulose  9004-65-3, Hydroxypropyl methylcellulose
      9004-67-5, Methylcellulose  9005-25-8, Starch, biological studies
      9005-32-7, Alginic acid  9005-37-2, Propylene glycol alginate
      9005-38-3, Sodium alginate  9050-04-8  9050-36-6, Maltodextrin
      9063-38-1, Sodium starch glycolate  11138-66-2, Xanthan gum  14807-96-6,
      Talc, biological studies  22839-47-0, Aspartame  25013-16-5, Butylated
      hydroxyanisole  25322-68-3, Polyethylene glycol  36653-82-4, Cetyl
      alcohol  39404-33-6, Dextrates  54182-62-6D, Polacrilin, potassium form
      74811-65-7, Croscarmellose sodium  84057-84-1, Lamotrigine
      RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
         (pharmaceutical composition containing lamotrigine particles of defined
morphol.
         and excipients)

ALL ANSWERS HAVE BEEN SCANNED

=> d his
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     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

     FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1             STRUCTURE UPLOADED
L2             3 S L1 SSS SAM
L3           128 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4            25 S L3/P
                E US20050238724/PN,PRN,AN
L5             0 S E3/RN
L6             1 S E3

=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                    78.55      257.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY     SESSION
CA SUBSCRIBER PRICE                                   -19.50      -19.50

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
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STRUCTURE FILE UPDATES:    3 APR 2007  HIGHEST RN 929074-02-2
DICTIONARY FILE UPDATES:   3 APR 2007  HIGHEST RN 929074-02-2

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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s l6
L7             0 US2005238724/PN

=> d his

     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

     FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1             STRUCTURE UPLOADED
L2             3 S L1 SSS SAM
L3           128 S L1 SSS FULL
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     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4             25 S L3/P
                E US20050238724/PN,PRN,AN
L5              0 S E3/RN
L6              1 S E3

     FILE 'REGISTRY' ENTERED AT 16:52:38 ON 04 APR 2007
L7              0 S L6

=> fil hcaplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                  ENTRY     SESSION
FULL ESTIMATED COST                                5.85      263.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                  ENTRY     SESSION
CA SUBSCRIBER PRICE                                0.00      -19.50

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 4 Apr 2007  VOL 146 ISS 15
FILE LAST UPDATED: 3 Apr 2007  (20070403/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s lamotrigine/cn
    REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.



L9         1265 L8

=> s "3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine"
       6859857 "3"
       6355474 "5"
```





```
         35536 "DIAMINO"
             3 "DIAMINOS"
         35536 "DIAMINO"
                 ("DIAMINO" OR "DIAMINOS")
       3871969 "6"
       9105408 "2"
       6859857 "3"
         15029 "DICHLOROPHENYL"
       9078625 "1"
       9105408 "2"
       5555409 "4"
         41884 "TRIAZINE"
         10234 "TRIAZINES"
         44464 "TRIAZINE"
                 ("TRIAZINE" OR "TRIAZINES")
L10         27 "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"
                 ("3"(W)"5"(W)"DIAMINO"(W)"6"(W)"2"(W)"3"(W)"DICHLOROPHENYL"(W)
                 "1"(W)"2"(W)"4"(W)"TRIAZINE")

=> d scan l10 1-5
'1-5' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC    ICM  C07D253-06
      ICS  A61K031-53
CC    28-19 (Heterocyclic Compounds (More Than One Hetero Atom))
      Section cross-reference(s): 1, 63
TI    Preparation of 3,5-diamino-6-(
      2,3-dichlorophenyl)-1,2,
      4-triazine isethionate as an antiepileptic
ST    aminodichlorophenyltriazine  isethionate prepn anticonvulsant; triazine
      diaminodichlorophenyl  isethionate prepn anticonvulsant
IT    Anticonvulsants and Antiepileptics
         (diamino(dichlorophenyl)triazine.isethionate)
IT    6574-97-6, 2,3-Dichlorophenyl cyanide
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (cyclocondensation of, with aminoguanidine)
IT    2582-30-1, Aminoguanidine bicarbonate
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (cyclocondensation of, with dichlorophenyl cyanide)
IT    84057-84-1P
      RL: SPN (Synthetic preparation); PREP (Preparation)
         (preparation and conversion of, into isethionate salt)
IT    113170-86-8P
      RL: BAC (Biological activity or effector, except adverse); BSU (Biological
      study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
      BIOL (Biological study); PREP (Preparation); USES (Uses)
         (preparation of, as anticonvulsant)
IT    107-36-8, Isethionic acid
      RL: PROC (Process)
         (salt formation of, with diaminotriazine derivative)


The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
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CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
CLASS ------- IPC, NCL, ECLA, FTERM
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, CLASS

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field
codes.  For a list of the display field codes, enter HELP DFIELDS at
an arrow prompt (=>).  Examples of formats include: TI; TI,AU; BIB,ST;
TI,IND; TI,SO.  You may specify the format fields in any order and the
information will be displayed in the same order as the format
specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR,
FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):ide
'IDE' IS NOT VALID HERE

To display more answers, enter the number of answers you would like to
see.  To end the display, enter "NONE", "N", "0", or "END".
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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):5

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC    ICM  A61K031-00
      ICS  C07D263-32
TI    Process for the preparation of 3,5-diamino-
      6-(2,3- dichlorophenyl)-1,
      2,4-triazine

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
CC    75 (Crystallography and Liquid Crystals)
TI    Lamotrigine dimethylformamide sesquisolvate

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
CC    25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
TI    Synthesis of 2,3-Dichlorobenzonitrile
ST    dichloroaniline diazotization; dichlorophenyldiazinium  prepn Sandmeyer
      reaction; dichlorobenzonitrile prepn
IT    Substitution reaction
         (Sandmeyer; preparation of dichlorobenzonitrile via diazotization of
         dichloroaniline followed by Sandmeyer reaction)
IT    608-27-5, 2,3-Dichloroaniline
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (preparation of dichlorobenzonitrile via diazotization of dichloroaniline
         followed by Sandmeyer reaction)
IT    73260-77-2P
      RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
      (Reactant or reagent)
         (preparation of dichlorobenzonitrile via diazotization of dichloroaniline
         followed by Sandmeyer reaction)
IT    6574-97-6P, 2,3-Dichlorobenzonitrile
      RL: SPN (Synthetic preparation); PREP (Preparation)
         (preparation of dichlorobenzonitrile via diazotization of dichloroaniline
         followed by Sandmeyer reaction)

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC    ICM  C07C281-18
CC    28-19 (Heterocyclic Compounds (More Than One Hetero Atom))
      Section cross-reference(s): 45
TI    Process for preparing 2-(2,3-dichlorophenyl)-2-
      (aminoguanidine)acetonitrile  and a process for its cyclization into
      3,5-diamino-6-(2,3
      -dichlorophenyl)-1,2,4-
      triazine
ST    diaminodichlorophenyltriazine  prepn cyclization
      dichlorophenylaminoguanidineacetonitrile
IT    Alcohols, uses
      RL: NUU (Other use, unclassified); USES (Uses)
         (aliphatic, solvents; in the cyclization of 2-(2,3-dichlorophenyl)-2-
         (aminoguanidine)acetonitrile  into 3,5-
         diamino-6-(2,3-
         dichlorophenyl)-1,2,4-
         triazine)
IT    Condensation reaction catalysts
         (methanesulfonic acid; for the conversion of 2,3-dichlorobenzoyl
         cyanide with aminoguanidine bicarbonate in a non-aqueous medium to give
         2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)
IT    Condensation reaction
         (of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a
```

non-aqueous medium in the presence of methanesulfonic acid to give 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)

IT Cyclization
(of 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)

IT 75-75-2, Methanesulfonic acid
RL: CAT (Catalyst use); USES (Uses)
(condensation catalyst; in a process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile from 2,3-dichlorobenzoyl cyanide and aminoguanidine bicarbonate)

IT 2582-30-1, Aminoguanidine bicarbonate 77668-42-9, 2,3-Dichlorobenzoyl cyanide
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)

IT 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(in the condensation of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a non-aqueous medium in the presence of methanesulfonic acid to give 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)

IT 84689-20-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)

IT 84057-84-1P, 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)

IT 64-17-5, Ethanol, uses 67-63-0, Isopropanol, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in the cyclization of 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)

L10 27 ANSWERS HCAPLUS COPYRIGHT 2007 ACS on STN
CC 1-2 (Pharmacology)
TI Transplacental passage of lamotrigine in a human placental perfusion system in vitro and in maternal and cord blood in vivo
ST lamotrigine anticonvulsant bioavailability placenta perfusion pregnancy fetus epilepsy
IT Embryo, animal
(fetus; lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)
IT Anticonvulsants
Drug bioavailability





Epilepsy
Human
Perfusion
Placenta
Pregnancy
(lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)

IT Biological transport
(uptake; lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)

IT 84057-84-1, Lamotrigine
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)

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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d his

     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

     FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1             STRUCTURE UPLOADED
L2               3 S L1 SSS SAM
L3             126 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4              25 S L3/P
                E US20050238724/PN,PRN,AN
L5               0 S E3/RN
L6               1 S E3

     FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7               0 S L6

     FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
                E LAMOTRIGINE+ALL/CT
                S LAMOTRIGINE/CN

     FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8               1 S LAMOTRIGINE/CN

     FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9            1265 S L8
L10             27 S 3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE*

=> d l10 1-27 ibib abs

L10 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2007:365185 HCAPLUS
TITLE:                   Process for the preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S):             Rawalnath, Sakhardande Rajiv; Kanji, Khatri Navin; Nilkanth, Firake Pandharinath; Vasant, Panchal Rajesh; Nagesh, Barekar Chandan; Madhukar, Mohite Dhanaji
PATENT ASSIGNEE(S):      Saxena, Alok, India
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SOURCE:                  Indian Pat. Appl.
                         CODEN: INXXBQ
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ------------------  ----   --------    --------------------   --------
     IN 2006MU00071       A     20060421    IN 2006-MU71           20060117
PRIORITY APPLN. INFO.:                      IN 2006-MU71           20060117
AB   There is disclosed an improved process for the preparation of 3,5- diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine which process comprises the step of reacting 2,3-dichlorobenzoylchloride with cuprous cyanide in presence of acetonitrile without the need of a co solvent to obtain dichlorbenzoyl cyanide, said dichlorobenzoyl cyanide is reacted with amino guanidine bicarbonate to produce a schiff;s base, which is cyclized in presence of aqueous potassium hydroxide to produce 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

L10 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2007:40805 HCAPLUS
TITLE:                   Crystal structure of lamotriginium hydrogen phthalate dimethylformamide solvate (1:1:1)
AUTHOR(S):               Sridhar, Balasubramanian; Ravikumar, Krishnan
CORPORATE SOURCE:        Lab. X-ray Crystallography, Indian Inst. Chemical Technology, Hyderabad, India
SOURCE:                  Molecular Crystals and Liquid Crystals (2006), 461, 131-141
                         CODEN: MCLCD8; ISSN: 1542-1406
PUBLISHER:               Taylor & Francis, Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The title compound, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine-hydrogen phthalate-dimethylformamide, C9H8N5Cl2·C8H5O4·C3H7NO (lamophthalate), crystallizes in the triclinic space group P1 with unit cell parameters a = 10.1587(6) Å, b = 11.3704(7) Å, c = 12.1976(7) Å, α = 110.797(1)°, β = 111.61(1)°, γ = 99.53(1)°, V = 1151.16(12) Å3, and Z = 2. The asym. unit comprises one lamotriginium cation, one hydrogen phthalate anion, and one DMF solvate. The dihedral angle between the two planar rings is 65.3(1)°. The expected proton transfer occurs at N2 of the triazine ring. Both O-H...O and N-H...O hydrogen bonding stabilizes the crystal structure.
REFERENCE COUNT:        17    THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2006:1032885 HCAPLUS
TITLE:                   Lamotrigine dimethylformamide sesquisolvate
AUTHOR(S):               Sridhar, Balasubramanian; Ravikumar, Krishnan
CORPORATE SOURCE:        Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
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SOURCE:                  Acta Crystallographica, Section E: Structure Reports Online (2006), E62(10), o4752-o4754
                         CODEN: ACSEBH; ISSN: 1600-5368
                         URL: http://journals.iucr.org/e/issues/2006/10/00/is2071/index.html
PUBLISHER:               Blackwell Publishing Ltd.
DOCUMENT TYPE:           Journal; (online computer file)
LANGUAGE:                English
AB   In the title compound, C9H7N5Cl2·1.5C3H7NO, the asym. unit consists of two crystallog. independent lamotrigine (systematic name: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) and three DMF mols. In the crystal structure, N-H···N and N-H···O hydrogen bonds lead to the formation of R22(8) and R23(8) motifs.
REFERENCE COUNT:         14    THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2005:421792 HCAPLUS
DOCUMENT NUMBER:         142:430313
TITLE:                   Process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (Lamotrigine) via reaction of 2,3-dichlorobenzoyl chloride with cuprous cyanide and then with aminoguanidine bicarbonate followed by cyclization.
INVENTOR(S):             Vyas, Sharad Kumar
PATENT ASSIGNEE(S):      Torrent Pharmaceuticals Ltd., India
SOURCE:                  Indian, 12 pp.
                         CODEN: INXXAP
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ------------------  ----   --------    --------------------   --------
     IN 183150            A1    19990925    IN 1998-CA2171         19981214
     CA 2334937           A1    20000622    CA 1999-2334937        19991207
     CA 2334937           C     20040921
     WO 2000035888        A1    20000622    WO 1999-IB1955         19991207
          W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ
          RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 2000012924        A     20000703    AU 2000-12924          19991207
     EP 1140872           A1    20011010    EP 1999-956293         19991207
     EP 1140872           B1    20030917
          R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
     AT 250041            T     20031015    AT 1999-956293         19991207
     RU 2231526           C2    20040627    RU 2001-115698         19991207
     US 6111101           A     20000829    US 1999-456501         19991208
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PRIORITY APPLN. INFO.: IN 1998-CA2171 A 19981214
WO 1999-IB1955 W 19991207
OTHER SOURCE(S): CASREACT 142:430313
AB Lamotrigine was prepared by reaction of 2,3-dichlorobenzoyl chloride with CuCN (1:1-2 molar ratio) in MeCN and a cosolvent to produce dichlorobenzoyl cyanide, reaction of the latter with aminoguanidine bicarbonate to produce the cyanoimine intermediate 2-[cyano(2,3-dichlorophenyl)methylene]hydrazinecarboximidamide, and cyclization of this in the presence of aqueous KOH at 80°-reflux.

L10 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1063399 HCAPLUS
DOCUMENT NUMBER: 143:326054
TITLE: Synthesis of 2,3-Dichlorobenzonitrile
AUTHOR(S): Deng, Hong; Liao, Qi; Zhou, Ying
CORPORATE SOURCE: Dept. of Chemistry, Central South Forestry University, Zhuzhou, Hunan Province, 412006, Peop. Rep. China
SOURCE: Jingxi Huagong Zhongjianti (2004), 34(5), 23-24
CODEN: JHZIAR; ISSN: 1009-9212
PUBLISHER: Jingxi Huagong Zhongjianti Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 143:326054
AB 2,3-Dichlorobenzonitrile was the important intermediate for synthesizing 2,3-dichlorobenzoic acid, which is the key intermediate for synthesizing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, the specific antiepileptic called Lamotrigine. 2,3-Dichlorobenzonitrile was synthesized from 2,3-dichloroaniline by diazo and Sandmeyer reaction. The yield was over 60%.

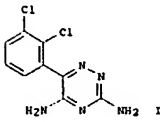
L10 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:421470 HCAPLUS
DOCUMENT NUMBER: 141:7119
TITLE: Preparation of crystalline lamotrigine and its monohydrate
INVENTOR(S): Manjunatha, Sulur G.; Kulkarni, Ashok Krishna; Kishore, Charugundla; Bokka, Ravisankar
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: Brit. UK Pat. Appl., 25 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| GB 2395483 | A | 20040526 | GB 2003-15608 | 20030703 |
| WO 2005003104 | A2 | 20050113 | WO 2004-IN186 | 20040628 |
| WO 2005003104 | A3 | 20050922 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, | | | | |





ES, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: GB 2003-15608 A 20030703
OTHER SOURCE(S): CASREACT 141:7119
GI



I

AB The invention relates to crystalline lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) (I) monohydrate and anhydrous lamotrigine. An improved process for manufacturing these products comprises reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in aqueous mineral acid, optionally together with a water miscible organic solvent, at 30-80° to produce the 2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (Schiff base) (II). The Schiff base II is further cyclized in aqueous organic solvent, e.g. alc. to produce pure lamotrigine of a pharmaceutically acceptable quality which on further drying at 45-50° under vacuum yields lamotrigine monohydrate, and/or on further drying at 100-110° yields anhydrous lamotrigine. The lamotrigine monohydrate or anhydrous lamotrigine thereby produced may then be brought into association with a pharmaceutically acceptable carrier for administration to a patient in need thereof.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:390214 HCAPLUS
DOCUMENT NUMBER: 140:391299
TITLE: Process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Dalmases Barjoan, Pere; Bessa Bellmunt, Jordi
PATENT ASSIGNEE(S): Laboratorios Vita, S.A., Spain
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004039767 | A1 | 20040513 | WO 2003-IB4763 | 20031027 |

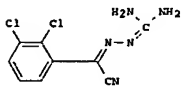




W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| ES 2209639 | A1 | 20040616 | ES 2002-2502 | 20021031 |
| ES 2209639 | B1 | 20050801 | | |
| AU 2003272019 | A1 | 20040525 | AU 2003-272019 | 20031027 |
| EP 1556341 | A1 | 20050727 | EP 2003-753860 | 20031027 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2006052625 | A1 | 20060309 | US 2005-532397 | 20050422 |
| US 7179913 | B2 | 20070220 | | |
| NO 2005002574 | A | 20050527 | NO 2005-2574 | 20050527 |

PRIORITY APPLN. INFO.: ES 2002-2502 A 20021031
WO 2003-IB4763 W 20031027
OTHER SOURCE(S): CASREACT 140:391299
GI



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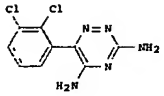


II

AB A method for preparing the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile (I; m.p. 180-183°) which comprises the condensation reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a non-aqueous medium in the presence of methanesulfonic acid, which produces good I yields and short reaction times. I is cyclized into 3,5-diamino-6-(2,3





-dichlorophenyl)-1,2,4-triazine (II; m.p. 217°) under reflux in an aliph alc. (e.g., ethanol) or alc.-water mixture
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:267313 HCAPLUS
DOCUMENT NUMBER: 140:303705
TITLE: Two-step process for the synthesis of high-purity 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine from 2,3-dichlorobenzoyl cyanide and aminoguanidine dimesylate
INVENTOR(S): Neu, Jozsef; Gizur, Tibor; Toerley, Jozsef; Csabai, Janos; Vegh, Ferenc; Kalvin, Peter; Tarkanyi, Gabor
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004026845 | A1 | 20040401 | WO 2003-HU72 | 20030918 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| HU 200203114 | A2 | 20040528 | HU 2002-3114 | 20020920 |
| CA 2498761 | A1 | 20040401 | CA 2003-2498761 | 20030918 |
| AU 2003267676 | A1 | 20040408 | AU 2003-267676 | 20030918 |
| EP 1539720 | A1 | 20050615 | EP 2003-748368 | 20030918 |
| EP 1539720 | B1 | 20061122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| AT 346051 | T | 20061215 | AT 2003-748368 | 20030918 |
| IN 2005KN00267 | A | 20060714 | IN 2005-KN267 | 20050224 |
| US 2006178511 | A1 | 20060810 | US 2005-528379 | 20050329 |
| | | | HU 2002-3114 A | 20020920 |
| | | | WO 2003-HU72 W | 20030918 |

PRIORITY APPLN. INFO.:
OTHER SOURCE(S): CASREACT 140:303705
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB High-purity 3,5-diamino-6-(

2,3-dichlorophenyl)-1,2,
4-triazine (I; i.e., lamotrigine) is prepared by the
condensation reaction of 2,3-dichlorobenzoyl cyanide (II) with 1-2 mol
equivalent of an aminoguanidine salt (e.g., aminoguanidine dimesylate) in 3-6
mol equivalent of methanesulfonic acid, then the obtained adduct (III) is
transformed without isolation into the desired product by contacting it
with magnesium oxide, followed by crystallization of the product from an
appropriate organic solvent (e.g., acetone).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:159133 HCAPLUS
DOCUMENT NUMBER: 139:316547
TITLE: Transplacental passage of lamotrigine in a human placental perfusion system in vitro and in maternal and cord blood in vivo
AUTHOR(S): Myllynen, Paeivi K.; Pienimaeki, Paeivi K.; Vaehaekangas, Kirsi H.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Oulu, PO Box 5000, Oulu, FIN-90014, Finland
SOURCE: European Journal of Clinical Pharmacology (2003), 58(10), 677-682
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied transplacental passage of lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine; LTG) using an ex vivo human placental perfusion method and in in vivo samples. Term placentae from healthy mothers without medications were perfused in a recirculating dual perfusion system. LTG (2.5 μg/mL, n = 4; 10 μg/mL, n = 4) and reference compound antipyrine (100 μg/mL) were added into the maternal circulation. The disappearance of drugs from the maternal circulation and appearance into the fetal circulation was followed every 15 min up to 2 h. Drug concns. were analyzed using high-performance liquid chromatog. In addition to human placental perfusions, we analyzed LTG concns. in maternal vein and cord blood samples after delivery from two epileptic mothers receiving LTG therapy during pregnancy. LTG was detectable in the fetal circulation at 15 min in all of the perfusions, indicating rapid transfer. Maternal and fetal concns. reached equilibrium at 60 min with both concns. used. The feto-maternal ratio was 1.26 ± 0.20 with 10 μg/mL LTG and 0.83 ± 0.41 with 2.5 μg/mL LTG at the end of the perfusion. The transfer of LTG from the maternal to the fetal compartment at 120 min was 28.9 ± 10.7% with 2.5 μg/mL LTG and 37.8 ± 3.2% with 10 μg/mL LTG (p > 0.05). In the serum samples from epileptic mothers, the cord blood maternal concentration ratio was 1.02 in one pair and 1.55 in the other. LTG crossed the placenta easily and rapidly, indicating that the maternal treatment leads to a considerable fetal exposure.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:76761 HCAPLUS
DOCUMENT NUMBER: 138:137336
TITLE: Method for producing lamotrigine from alpha-oxo-2,3-dichlorophenylacetamidinoaminoguanidino





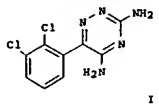
hydrazone by ring closure reaction
INVENTOR(S): Schneider, Geza; Gegoe, Csaba Lehel; Ondi, Levente; Mate, Attila Gergely; Lukacs, Ferenc; Nyerges, Miklos; Garaczi, Sandor
PATENT ASSIGNEE(S): Hela AG, Germany; CF Pharma Gyogyszergyarto Kft.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003008393 | A1 | 20030130 | WO 2002-EP7433 | 20020704 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10134980 | A1 | 20030213 | DE 2001-10134980 | 20010717 |
| DE 10134980 | C2 | 20030528 | | |
| EP 1311492 | A1 | 20030521 | EP 2002-758308 | 20020704 |
| EP 1311492 | B1 | 20040908 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE | | | | |
| CA 2417435 | C | 20040113 | CA 2002-2417435 | 20020704 |
| CA 2417435 | A1 | 20030130 | | |
| ES 2224074 | T3 | 20050301 | ES 2002-2758308 | 20020704 |
| US 2003191310 | A1 | 20031009 | US 2003-343225 | 20030515 |
| US 6683182 | B2 | 20040127 | | |

PRIORITY APPLN. INFO.: DE 2001-10134980 A 20010717
WO 2002-EP7433 W 20020704
OTHER SOURCE(S): CASREACT 138:137336; MARPAT 138:137336
GI







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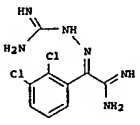

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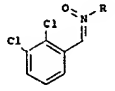

III

AB The invention relates to a method for producing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine [lamotrigine (I)], or its pharmaceutically acceptable salts, by ring closure reaction from α-oxo-2,3-dichlorophenylacetamidinoaminoguanidino hydrazone (II) or its salts. The preparation of II from N-oxides, III [R = linear, branched or cyclic (un)substituted alkyl, aryl, aralkyl], or their salts, are also described. Thus, I was prepared from 2,3-Cl2C6H3CH:N(O)Ph, via cyanation with NaCN, amination to the acetamidine hydrochloride, reaction with aminoguanine bicarbonate to give II·HCl, treatment with aqueous NaOH to give the free base, which is cyclized to I; cyclization of II·HCl gives I·HCl.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:775487 HCAPLUS
DOCUMENT NUMBER: 138:60875
TITLE: Development of a solid phase extraction protocol for the simultaneous determination of anthracene and its oxidation products in surface waters by reversed-phase HPLC
AUTHOR(S): Papadoyannis, I. N.; Zotou, A.; Samanidou, V. F.
CORPORATE SOURCE: Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki, GR-541 24, Greece
SOURCE: Journal of Liquid Chromatography & Related Technologies (2002), 25(17), 2635-2653
CODEN: JLCTFC; ISSN: 1082-6076
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A gradient reversed-phase HPLC (RP-HPLC) method for the simultaneous determination





of anthracene, anthraquinone, and 1-hydroxyanthraquinone, with photodiode array detection at 250 nm, was developed. The separation was achieved on a Kromasil 100 G8 5 μm 250 × 4 mm column, applying a 10-min linear gradient elution starting with 85% methanol and 15% 0.05M ammonium acetate and ending up with 95% of methanol and 5% 0.05M ammonium acetate, at a flow-rate 0.7 mL/min, using 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) as internal standard Calibration curves were rectilinear for 0.1-3.0 ng anthracene, 0.1-10.0 ng anthraquinone, and 0.5-20.0 ng 1-hydroxyanthraquinone, when 10 μL was injected. The detection limits were 0.05 ng injected on-column for anthracene and anthraquinone and 0.3 ng on-column for 1-hydroxyanthraquinone. The average intra- and inter-day RSDs for injection precision (in terms of peak area) were 1.9% and 3.62%, resp. The method was applied to the anal. of river and lake waters. A protocol, combining solid phase extraction (SPE) with sonication of matrix with sorbent, was developed for enhancement of recovery. The proposed protocol was chosen among other studied, after optimization of each step. Mean recoveries were 50% for anthracene, 71% for anthraquinone, and 105% for 1-hydroxy anthraquinone.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:435163 HCAPLUS
DOCUMENT NUMBER: 133:160143
TITLE: Evidence that DHPG-induced nociception depends on glutamate release from primary afferent C-fibres
AUTHOR(S): Lefebvre, Celeste; Fisher, Kim; Cahill, Catherine M.; Coderre, Terence J.
CORPORATE SOURCE: Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: NeuroReport (2000), 11(8), 1631-1635
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors examined whether enhanced glutamate release contributes to the expression of persistent spontaneous nociceptive behaviors (SNBs) in rats induced by intrathecal (i.t.) administration of the selective group I mGluR agonist, (RS)-3,5-dihydroxyphenylglycine ((RS)-DHPG). Pretreatment with drugs that have been shown to inhibit glutamate release, including a group II metabotropic glutamate receptor (mGluR) agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate ((2R,4R)-APDC), a group III mGluR agonist L-2-amino-4-phosphonobutyrate (L-AP4), or the use-dependent sodium channel blockers 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) and 2-amino-6-trifluoromethoxybenzothiazole (riluzole), produced dose-dependent reductions in (RS)-DHPG-induced SNBs. The authors have also shown that incubation of rat lumbar spinal cord slices with (RS)-DHPG potentiates 4-aminopyridine-evoked (4-AP) release of glutamate. Furthermore, the authors found that destruction of unmyelinated primary afferent C-fibers by neonatal capsaicin treatment significantly reduced (RS)-DHPG-induced SNBs in adult rats. Together, these results suggest that (RS)-DHPG-induced nociception is dependent on spinal glutamate release, probably from primary afferent C-fibers.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:421116 HCAPLUS
DOCUMENT NUMBER: 133:60362
TITLE: An improved process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |
| PRIORITY APPLN. INFO.: | | | IN 1998-CA2171 A | 19981214 |
| | | | WO 1999-IB1955 W | 19991207 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) (I) useful as antiepileptic drug (no data) is prepared in a 3 step process. Thus, 2,3-dichlorobenzoylchloride was treated with cuprous cyanide in presence of acetonitrile and a solvent to produce 2,3-dichlorobenzoyl cyanide, further with aminoguanidine and cyclized to produce I.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:12098 HCAPLUS
DOCUMENT NUMBER: 132:130210
TITLE: Structure of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate solvate (lamotrigine isethionate)
AUTHOR(S): Potter, Brian; Palmer, Rex A.; Withnall, Robert;





Leach, Michael J.; Chowdhry, Babur Z.
CORPORATE SOURCE: Department of Crystallography, Birkbeck College, University of London, London, WC1E 7HX, UK
SOURCE: Journal of Chemical Crystallography (1999), 29(6), 701-706
CODEN: JCCYEV; ISSN: 1074-1542
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The crystal and mol. structure of lamotrigine isethionate was determined by direct methods. The compound crystallizes in the tetragonal space group I41/a, with a 19.684(5), c 16.557(5) Å; Z = 16, dc = 1.579; R = 0.0532, Rw = 0.1317 for 2041 reflections. Atomic coordinates are given. The isethionate moiety forms multiple H bonds to the lamotrigine nucleus, three from one isethionate, two from a symmetry related isethionate and a further two from two different symmetry related mols. Protonation of N(2') in the triazine ring, not observed in the native lamotrigine structure is presumably associated with the interaction of the isethionate moiety. Both rings in the lamotrigine moiety are essentially planar, with a dihedral angle of 66.08(7)° compared to 80.70° in native lamotrigine. The connecting bond length C(1)-C(6') 1.493(3) Å also correlates well with values in related compds. (1.480(3) Å) in the native structures.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:682978 HCAPLUS
DOCUMENT NUMBER: 132:98214
TITLE: Detection of the principal synthetic route indicative impurity in lamotrigine
AUTHOR(S): Ashton, D. S.; Ray, A. D.; Velko, K.
CORPORATE SOURCE: School of Pharmacy, University of London, London, UK
SOURCE: International Journal of Pharmaceutics (1999), 189(2), 241-248
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An anal. method has been developed for the detection of trace amts. of the principal synthetic route indicative impurity in lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine). A sample extract was preconcd. by normal-phase high-performance liquid chromatog. (HPLC) and analyzed by subsequent online reversed-phase HPLC-thermospray mass spectrometry (TSP-MS). During the sample extraction and concentration step, carried out by semipreparative normal-phase chromatog., the preliminary separation of the impurity from the lamotrigine takes place. The organic solvent (dichloroethane-methanol, 90:10, volume/volume) is evaporated from the collected fraction and the material is redissolved in a smaller volume of the reversed-phase mobile phase. The collected fraction is then subjected to reversed-phase HPLC-TSP-MS. The influence of an ultrasonic extraction step has been examined. When the method was applied to lamotrigine tablets, a shake flask partitioning step using 1 mg/mL EDTA in water-dichloroethane was used instead of the ultrasonic extraction. Detection limit and recovery measurements showed that the route indicative impurity formed during the synthesis could be detected in the 50-100 ppb (weight/weight)





range.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:289572 HCAPLUS
DOCUMENT NUMBER: 127:636
TITLE: A calcium antagonistic effect of the new antiepileptic drug lamotrigine
AUTHOR(S): v. Wegerer, J.; Hesslinger, B.; Berger, M.; Walden, J.
CORPORATE SOURCE: Universitaet Freiburg, Abt. Psychiatrie und Psychotherapie, Hauptstr. 5, 79104, Freiburg, Germany
SOURCE: European Neuropsychopharmacology (1997), 7(2), 77-81
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The new antiepileptic drug lamotrigine (LTG; 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) has been shown to be effective in the treatment of focal epilepsies with or without secondary generalization. Furthermore, some case reports indicate an efficacy in the treatment of bipolar affective disorders. It has been suggested that the main mechanism of action of LTG is the inhibition of glutamate release through blockade of voltage sensitive sodium channels and stabilization of the neuronal membrane. Since some antidepressant drugs and the antiepileptic substance carbamazepine have calcium antagonistic properties, which may be of significance in the pathophysiol. of epilepsies and affective disorders, the interaction of lamotrigine with carbamazepine and the organic calcium channel blocker verapamil was analyzed in the low Mg2+-induced model epilepsy which has been shown to be suppressed specifically by organic calcium antagonists. Lamotrigine reduced the frequency of occurrence of low-magnesium induced field potentials in CA1 and CA3 areas of the hippocampus slice preparation (guinea pigs) in a dose-dependent manner. The subthreshold concns. which yielded no effect were 1 μmol/L for lamotrigine, 10 μmol/L for carbamazepine and 2 μmol/L for verapamil. Combinations of these subthreshold concns. elicited a reduction in the repetition rate of field potentials. The results indicate that lamotrigine behaves additive with verapamil and carbamazepine what can be due to a common action on the same subtype of calcium channels. It can be assumed that lamotrigine may have besides its action on high-frequency sodium dependent action potentials also effects on calcium channels.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:288924 HCAPLUS
DOCUMENT NUMBER: 126:312094
TITLE: Effects of lamotrigine on brain nitrite and cGMP levels during focal cerebral ischemia in rats
AUTHOR(S): Balkan, S.; Ozben, T.; Balkan, E.; Oguz, N.; Serteser, M.; Gumuslu, S.
CORPORATE SOURCE: Department of Neurology, School of Medicine, Akdeniz University, Antalya, 07070, Turk.
SOURCE: Acta Neurologica Scandinavica (1997), 95(3), 140-146
CODEN: ANRSAS; ISSN: 0001-6314
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal





LANGUAGE: English
AB Glutamate receptor antagonists are protective in animal models of focal cerebral ischemia. Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an anticonvulsant drug that blocks voltage-gated sodium channels and inhibits the ischemia-induced release of glutamate. Expts. in primary neuronal cultures implicate nitric oxide (NO) as a mediator of glutamatergic neurotoxicity acting via N-Methyl-D-Asparate (NMDA) receptors. The effect of glutamate release inhibitor, lamotrigine, upon NO and cGMP production has been examined in focal cerebral ischemia in rats. Focal cerebral ischemia was produced by the permanent occluaion of right middle cerebral artery (MCA) in urethane anesthetized rats. A number of indicators of brain NO production (nitrite, cGMP) were determined in ipsilateral and contralateral cerebral cortex and cerebellum after 0, 10, 60 min of focal cerebral ischemia. The same parameters were measured in rats treated with Lamotrigine (20 mg/kg, i.p.) 30 min before or just after the occluaion of the right MCA.

L10 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:546365 HCAPLUS
DOCUMENT NUMBER: 125:195693
TITLE: Preparation of lamotrigine.
INVENTOR(S): Lee, Grahame Roy
PATENT ASSIGNEE(S): Wellcome Foundation Limited, UK
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9620935 | A1 | 19960711 | WO 1995-GB3049 | 19951229 |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9643116 | A | 19960724 | AU 1996-43116 | 19951229 |
| EP 800521 | A1 | 19971015 | EP 1995-941818 | 19951229 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV | | | | |
| HU 77347 | A2 | 19980330 | HU 1997-1875 | 19951229 |
| JP 11507011 | T | 19990622 | JP 1995-520618 | 19951229 |
| RU 2162081 | C2 | 20010120 | RU 1997-112921 | 19951229 |
| FI 9702720 | A | 19970827 | FI 1997-2720 | 19970624 |
| US 5925755 | A | 19990720 | US 1997-836152 | 19970625 |
| PRIORITY APPLN. INFO.: | | | GB 1994-26448 A | 19941230 |
| | | | WO 1995-GB3049 W | 19951229 |

AB Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I), is prepared by treating 6-(2,3-dichlorophenyl)-5-chloro-3-thiomethyl-1,2,4-triazine (II) with NH3. Thus, II (preparation given) was heated with ethanolic NH3 in a sealed tube at 180° and 280 psi for 72 h to give I.

L10 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:186621 HCAPLUS
DOCUMENT NUMBER: 124:278888
TITLE: Inhibition of morphine withdrawal by lamotrigine: involvement of nitric oxide
AUTHOR(S): Lizasoain, Ignacio; Leza, Juan C.; Cuellar, Beatriz; Moro, Maria A.; Lorenzo, Pedro
CORPORATE SOURCE: Departamento de Farmacologia, Facultad de Medicina, Universidad Complutense de Madrid, Avenida Complutense s/n, Madrid, 28040, Spain
SOURCE: European Journal of Pharmacology (1996), 299(1-3), 41-5
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied the effects of lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine], a new antiepileptic compound, on naloxone-precipitated morphine withdrawal in mice. Pretreatment with lamotrigine (5-100 mg/kg, s.c.) reversed in a dose-dependent way the withdrawal-induced increase in cerebellar Ca2+-dependent nitric oxide (NO) synthase activity and reduced the number of escape jumps and other motor symptoms of abstinence, at doses that did not modify locomotor activity (25-50 mg/kg). Pretreatment with the NMDA receptor antagonist MK-801 [(+)-5-methyl-10,11-dihydroxy-5H-dibenzo[a,d]cyclohepten-5,10-imine; dizocilpine] (0.1-0.3 mg/kg, s.c.) also reversed the increase in cerebellar Ca2+-dependent NO synthase activity. However, although MK-801 reduced the number of escape jumps and other motor symptoms of abstinence, its effects were not clearly dose-dependent. Furthermore, the highest dose of MK-801 tested (0.3 mg/kg) caused an impairment of the locomotor behavior in naive mice. Thus, lamotrigine may represent a new and useful agent for the treatment of opiate abstinence.

L10 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:499316 HCAPLUS
DOCUMENT NUMBER: 123:699
TITLE: Cerebroprotective effect of lamotrigine after focal ischemia in rats
AUTHOR(S): Smith, Stuart E.; Meldrum, Brian S.
CORPORATE SOURCE: Department of Neurology, Institute of Psychiatry, Denmark Hill, SE5 8AF, UK
SOURCE: Stroke (1995), 26(1), 117-22
CODEN: SJCCA7; ISSN: 0039-2499
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamate receptor antagonists are protective in animal models of focal cerebral ischemia. Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl]-1,2,4-triazine) is an anticonvulsant drug that blocks voltage-gated sodium channels and inhibits the ischemia-induced release of glutamate. The cerebroprotective effect of lamotrigine (as the isethionate salt) after middle cerebral artery occlusion was described in rats. Neurol. deficit and infarct volume (visualized by the lack of reduction of 2,3,5-triphenyltetrazolium chloride) 24 h after permanent left middle cerebral artery occlusion were studied in Fischer rats (n=8 per group per dose). Lamotrigine at 20 mg/kg i.v. over





10 min administered immediately after middle cerebral artery occlusion reduced total infarct volume by 31% and cortical infarct volume by 52%. Lamotrigine at 8 mg/kg i.v. over 10 min reduced cortical infarct volume by 38%. Lamotrigine at 50 mg/kg i.v. for 10 min was not cerebroprotective and induced a decrease of 29±15 mm Hg in mean arterial blood pressure (P<.05, n=8). The optimum dose of lamotrigine (20 mg/kg i.v. over 10 min) when administered with a 1-h delay after middle cerebral artery occlusion reduced cortical infarct volume by 41%. Lamotrigine (20 mg/kg i.v. over 10 min) with a 2-h delay after middle cerebral artery occlusion was ineffective. Neurol. deficits after 24 h were improved after immediate treatment with lamotrigine at 20 mg/kg i.v. over 10 min.? The cerebroprotective effect of lamotrigine in rats is limited to a narrow dose range between 8 and 20 mg/kg. Lamotrigine or analogous compds. may be useful when given shortly after the onset of stroke.

L10 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:663729 HCAPLUS
DOCUMENT NUMBER: 121:263729
TITLE: Use of triazine compounds for the treatment of memory and learning disorders
INVENTOR(S): Baxter, Martin George
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9421260 | A1 | 19940929 | WO 1994-GB559 | 19940318 |
| W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9462176 | A | 19941011 | AU 1994-62176 | 19940318 |
| ZA 9401938 | A | 19950918 | ZA 1994-1938 | 19940318 |
| EP 689439 | A1 | 19960103 | EP 1994-909263 | 19940318 |
| EP 689439 | B1 | 20010124 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 08507782 | T | 19960820 | JP 1994-520807 | 19940318 |
| IL 109034 | A | 19981206 | IL 1994-109034 | 19940318 |
| AT 198831 | T | 20010115 | AT 1994-909263 | 19940318 |
| ES 2153854 | T3 | 20010316 | ES 1994-909263 | 19940318 |
| PT 689439 | T | 20010531 | PT 1994-909263 | 19940318 |
| US 5866597 | A | 19990202 | US 1997-900868 | 19970725 |
| GR 3035528 | T3 | 20010629 | GR 2001-400367 | 20010308 |
| PRIORITY APPLN. INFO.: | | | GB 1993-5693 | A 19930319 |
| | | | WO 1994-GB559 | W 19940318 |
| | | | US 1996-535140 | B1 19960328 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I) and its pharmaceutically acceptable acid addition salts can be used to treat impaired memory and learning disorders. Therapeutic effects of I were demonstrated in a scopolamine-induced mouse model of memory deficit and compared with those of ondansetron HCl and piracetam. A tablet containing 150 mg I was also formulated.





L10 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:663728 HCAPLUS
DOCUMENT NUMBER: 121:263728
TITLE: Use of triazine compounds as anxiolytics
INVENTOR(S): Critchley, Martyn Alan Edwin
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9421261 | A1 | 19940929 | WO 1994-GB560 | 19940318 |
| W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9462177 | A | 19941011 | AU 1994-62177 | 19940318 |
| ZA 9401939 | A | 19950918 | ZA 1994-1939 | 19940318 |
| EP 689440 | A1 | 19960103 | EP 1994-909264 | 19940318 |
| EP 689440 | B1 | 20000531 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 08507783 | T | 19960820 | JP 1994-520808 | 19940318 |
| JP 3633618 | B2 | 20050330 | | |
| AT 193446 | T | 20000615 | AT 1994-909264 | 19940318 |
| ES 2147232 | T3 | 20000901 | ES 1994-909264 | 19940318 |
| PT 689440 | T | 20001031 | PT 1994-909264 | 19940318 |
| US 5658905 | A | 19970819 | US 1995-535139 | 19950918 |
| GR 3033941 | T3 | 20001130 | GR 2000-401626 | 20000712 |
| PRIORITY APPLN. INFO.: | | | GB 1993-5692 | A 19930319 |
| | | | WO 1994-GB560 | W 19940318 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I) and its pharmaceutically acceptable acid addition salts can be used to treat anxiety and anxiety disorders. For example, an anxiolytic effect of I-isethionate was demonstrated with Vogel conflict model in rats. A tablet containing 150 mg I was also formulated.

L10 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:124865 HCAPLUS
DOCUMENT NUMBER: 120:124865
TITLE: Use of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate for the treatment and prevention of dependence on, tolerance to, and sensitization to drugs
INVENTOR(S): Nakamura-Craig, Meire
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1





PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9325207 | A1 | 19931223 | WO 1993-GB1243 | 19930611 |
| W: AU, CA, CZ, GB, JP, KR, NO, NZ, PL, RU, SK, UA, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9343452 | A | 19940104 | AU 1993-43452 | 19930611 |
| AU 688729 | B2 | 19980319 | | |
| EP 644763 | A1 | 19950329 | EP 1993-913346 | 19930611 |
| EP 644763 | B1 | 19970122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| GB 2282326 | A | 19950405 | GB 1994-23697 | 19930611 |
| JP 07507790 | T | 19950831 | JP 1993-501281 | 19930611 |
| AT 147980 | T | 19970215 | AT 1993-913346 | 19930611 |
| ES 2097516 | T3 | 19970401 | ES 1993-913346 | 19930611 |
| CZ 284061 | B6 | 19980812 | CZ 1994-3128 | 19930611 |
| IL 105986 | A | 19981206 | IL 1993-105986 | 19930611 |
| SK 279730 | B6 | 19990211 | SK 1994-1534 | 19930611 |
| HR 930964 | B1 | 20000630 | HR 1993-964 | 19930611 |
| JP 3439211 | B2 | 20030825 | JP 1994-501281 | 19930611 |
| US 5801171 | A | 19980901 | US 1994-347480 | 19941206 |
| NO 9404790 | A | 19941209 | NO 1994-4790 | 19941209 |
| PRIORITY APPLN. INFO.: | | | GB 1992-12495 | A 19920612 |
| | | | GB 1993-8654 | A 19930427 |
| | | | WO 1993-GB1243 | A 19930611 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4,-triazine (I) and its pharmaceutically and veterinarily acceptable salts (especially the ethionate) have activity in (a) preventing or reducing dependence on, and (b) preventing or reducing tolerance or reverse tolerance to, a dependence-inducing agent such as an opioid, a central nervous system depressant, a psychostimulant, or nicotine. Thus, I (5 mg/kg orally twice a day during morphine habituation) attenuated the development of morphine tolerance in rats without affecting the analgesic effect of morphine in the tail-flick test.

L10 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:617428 HCAPLUS
DOCUMENT NUMBER: 119:217428
TITLE: Use of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine for the treatment of pain and edema
INVENTOR(S): Nakamura-Craig, Meire; Leach, Michael John
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9316700 | A1 | 19930902 | WO 1993-GB341 | 19930218 |
| W: AU, CA, GB, JP, KR, NZ, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |

| | | | | | |
|---|---|---|---|---|---|
| AU 9335092 | A | 19930913 | AU 1993-35092 | | 19930218 |
| AU 684711 | B2 | 19980108 | | | |
| EP 626851 | A1 | 19941207 | EP 1993-904225 | | 19930218 |
| EP 626851 | B1 | 20010822 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | | |
| JP 07503968 | T | 19950427 | JP 1993-514628 | | 19930218 |
| JP 3713271 | B2 | 20051109 | | | |
| IL 104775 | A | 19970218 | IL 1993-104775 | | 19930218 |
| AT 204476 | T | 20010915 | AT 1993-904225 | | 19930218 |
| ES 2162813 | T3 | 20020116 | ES 1993-904225 | | 19930218 |
| PT 626851 | T | 20020228 | PT 1993-904225 | | 19930218 |
| CA 2129043 | C | 20040127 | CA 1993-2129043 | | 19930218 |
| GB 2277265 | A | 19941026 | GB 1994-14348 | | 19940715 |
| GB 2277265 | B | 19960110 | | | |
| US 5712277 | A | 19980127 | US 1996-680111 | | 19960715 |
| GR 3036958 | T3 | 20020131 | GR 2001-401827 | | 20011022 |
| PRIORITY APPLN. INFO.: | | | GB 1992-3483 | A | 19920219 |
| | | | NO 1993-GB341 | A | 19930218 |
| | | | US 1994-284497 | A1 | 19940804 |

AB The title compound (I) is useful in medicaments for the prevention or treatment of pain or edema. A tablet formulation containing I is given. I was tested in rats.

L10 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:126056 HCAPLUS
DOCUMENT NUMBER: 110:126056
TITLE: Structure of lamotrigine methanol solvate: 3 ,5-diamino-6-(2 ,3-dichlorophenyl)-1, 2,4-triazine-methanol, a novel anticonvulsant drug
AUTHOR(S): Janes, Robert W.; Liegarten, John N.; Palmer, Rex A.
CORPORATE SOURCE: Birkbeck Coll., Univ. London, London, WC1E 7HX, UK
SOURCE: Acta Crystallographica, Section C: Crystal Structure Communications (1989), C45(1), 129-32
CODEN: ACSCEE; ISSN: 0108-2701
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title compound is monoclinic, space group P21/n, with a 15.456(3), b 11.736(2), c 7.300(3) Å, and β 94.417(3)°; Z = 4 for dc = 1.449. The final R = 0.055 for 2444 reflections. Atomic coordinates are given. The Ph and triazine aromatic rings make a dihedral angle of 80.6(9)° with each other. The bond linking the 2 rings is 1.480(3) Å. The structure is stabilized by a network of H bonds involving amino and ring N atoms, one of the Cl atoms, and the MeOH of crystallization

L10 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:112505 HCAPLUS
DOCUMENT NUMBER: 108:112505
TITLE: Preparation of 3,5-diamino -6-(2,3- dichlorophenyl)-1,2, 4-triazine isethionate as an antiepileptic
INVENTOR(S): Sawyer, David Alan; Copp, Frederick Charles
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent





LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| EP 247892 | A1 | 19871202 | EP 1987-304776 | | 19870529 |
| EP 247892 | B1 | 19910424 | | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | | |
| DK 8702759 | A | 19871201 | DK 1987-2759 | | 19870529 |
| DK 166278 | B | 19930329 | | | |
| DK 166278 | C | 19930823 | | | |
| FI 8702406 | A | 19871201 | FI 1987-2406 | | 19870529 |
| FI 90770 | B | 19931215 | | | |
| FI 90770 | C | 19940325 | | | |
| AU 8773684 | A | 19871203 | AU 1987-73684 | | 19870529 |
| AU 597982 | B2 | 19900614 | | | |
| JP 62289570 | A | 19871216 | JP 1987-134772 | | 19870529 |
| JP 07051571 | B | 19950605 | | | |
| HU 45978 | A2 | 19880928 | HU 1987-2487 | | 19870529 |
| HU 196769 | B | 19890130 | | | |
| ZA 8703896 | A | 19890125 | ZA 1987-3896 | | 19870529 |
| US 4847249 | A | 19890711 | US 1987-56136 | | 19870529 |
| AT 62902 | T | 19910515 | AT 1987-304776 | | 19870529 |
| CA 1286670 | C | 19910723 | CA 1987-538395 | | 19870529 |
| IL 82710 | A | 19920115 | IL 1987-82710 | | 19870529 |
| PRIORITY APPLN. INFO.: | | | GB 1986-13183 | A | 19860530 |
| | | | EP 1987-304776 | A | 19870529 |

AB The title compound (I.isethionate), useful as an anticonvulsant (no data), was prepared by reaction of I with 2-hydroxyethanesulfonic acid (II) or by reaction of I salts with the anion of II. A 1.0 M solution of Na isethionate in H2O was passed through a column of IR 120 (H) ion exchange resin. I (preparation given) was added to the resulting II and the solution was filtered and evaporated Recrystn. from industrial methylated spirit gave 72% I.isethionate.

L10 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1985:542021 HCAPLUS
DOCUMENT NUMBER: 103:142021
TITLE: Triazine compounds having cardiovascular activity
INVENTOR(S): Allan, Geoffrey; Miller, Alastair Ainslie; Sawyer, David Alan
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 142106 | A2 | 19850522 | EP 1984-307374 | 19841026 |
| EP 142106 | A3 | 19861120 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| US 4649139 | A | 19870310 | US 1984-663682 | 19841022 |
| DK 8405121 | A | 19850428 | DK 1984-5121 | 19841026 |
| FI 8404212 | A | 19850428 | FI 1984-4212 | 19841026 |
| AU 8434758 | A | 19850509 | AU 1984-34758 | 19841026 |





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|---|---|---|---|---|---|
| AU 564667 | B2 | 19870820 | | | |
| JP 60109577 | A | 19850615 | JP 1984-225636 | | 19841026 |
| DD 224033 | A5 | 19850626 | DD 1984-268757 | | 19841026 |
| HU 36102 | A2 | 19850828 | HU 1984-4003 | | 19841026 |
| HU 191566 | B | 19870330 | | | |
| ES 537104 | A1 | 19860416 | ES 1984-537104 | | 19841026 |
| ZA 8408388 | A | 19860625 | ZA 1984-8388 | | 19841026 |
| SU 1371500 | A3 | 19880130 | SU 1984-3805251 | | 19841026 |
| IL 73332 | A | 19880630 | IL 1984-73332 | | 19841026 |
| PL 144899 | B1 | 19880730 | PL 1984-250213 | | 19841026 |
| CA 1261328 | A1 | 19890926 | CA 1984-466473 | | 19841026 |
| PRIORITY APPLN. INFO.: | | | GB 1983-28757 | A | 19831027 |
| OTHER SOURCE(S): | | MARPAT 103:142021 | | | |

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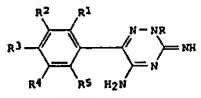

I

AB Tautomeric iminotriazinamines I [R = (un)substituted C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C3-10 cycloalkyl; R1-R5 = H, halogen, alkenyloxy, acyl, acyloxy, cyano, NO2, aryl, alkylthio, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, amino; R1R2, R2R3, R3R4, R4R5 = CH:CHCH:CH] were prepared Thus, 3,5-diamino-6-( 2,3-dichlorophenyl)-1,2, 4-triazine was alkylated with Me2CHI to give I-HI (R = Me2CH, R1 = R2 = Cl; R3-R5 = H) which was converted to the mesylate salt (II) (12% overall yield). II at 1 mg/kg i.v. to rats increased the amount of aconitine required to elicit ventricular arrhythmias by 490% compared with 84% for 1 mg/kg verapamil.

=> file reg

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 84.21 | 355.22 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -21.06 | -40.56 |

FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 3 APR 2007 HIGHEST RN 929074-02-2
DICTIONARY FILE UPDATES: 3 APR 2007 HIGHEST RN 929074-02-2





New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s 84057-84-1/rn
L11 1 84057-84-1/RN

=> d scan

L11 1 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-
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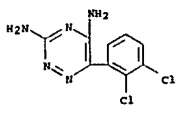
CI COM



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

ALL ANSWERS HAVE BEEN SCANNED

=> file hcaplus

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|---|---|---|
| FULL ESTIMATED COST | 0.45 | 355.67 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | 0.00 | -40.56 |

FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 4 Apr 2007 VOL 146 ISS 15
FILE LAST UPDATED: 3 Apr 2007 (20070403/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his

(FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1 STRUCTURE UPLOADED
L2 3 S L1 SSS SAM
L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4 25 S L3/P
E US20050238724/PN,PRN,AN
L5 0 S E3/RN
L6 1 S E3

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7 0 S L6

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
E LAMOTRIGINE+ALL/CT
S LAMOTRIGINE/CN

FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8 1 S LAMOTRIGINE/CN

FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9 1265 S L8
L10 27 S "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
L11 1 S 84057-84-1/RN

FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007

=> a l11
L12 1265 L11

=> a l10 or l12 and particle or granule
740429 PARTICLE
814603 PARTICLES
1234571 PARTICLE
(PARTICLE OR PARTICLES)
49055 GRANULE





86594 GRANULES
111146 GRANULE
(GRANULE OR GRANULES)
L13 111187 L10 OR L12 AND PARTICLE OR GRANULE

=> s l12 near particle
MISSING OPERATOR L12 NEAR
The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s l12 (n) particle
740429 PARTICLE
814603 PARTICLES
1234571 PARTICLE
(PARTICLE OR PARTICLES)
L14 0 L12 (A) PARTICLE

=> s l12 (w) particle
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1234571 PARTICLE
(PARTICLE OR PARTICLES)
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38387 CNS
L16 46 L12 AND CNS

=> d l16 1-46 ibib abs

L16 ANSWER 1 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:259513 HCAPLUS
DOCUMENT NUMBER: 146:302316
TITLE: 5-HT1B antagonist composition for treating CNS conditions
INVENTOR(S): Harrison, Wilma Marcia; Sobolov-Jaynes, Susan Beth; Foerster, Robert Sterling, Jr.; Van Beek, Jeroen Bernard
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 46pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007026219 | A2 | 20070308 | WO 2006-IB2364 | 20060821 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM





GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| JP 2007063277 | A | 20070315 | JP 2006-233101 | 20060830 |

PRIORITY APPLN. INFO.: US 2005-712954P P 20050831
AB The present invention relates to pharmaceutical compns. comprising 5-HT1B antagonists in combination with noradrenaline re-uptake inhibitor (NRI) or aerotonin noradrenaline reuptake inhibitor (SNRI) and optionally a pharmaceutically acceptable carrier, and to their medicinal use in treating or preventing CNS conditions such as depression, anxiety, cognitions, ADHD, and comorbid indications.

L16 ANSWER 2 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:226913 HCAPLUS
DOCUMENT NUMBER: 146:280994
TITLE: Reducing myocardial damage and the incidence of arrhythmia arising from loss, reduction or interruption in coronary blood flow
INVENTOR(S): Weiss, Steven Michael
PATENT ASSIGNEE(S): Australia
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007022568 | A1 | 20070301 | WO 2006-AU1207 | 20060824 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: AU 2005-904615 A 20050825
AB A method and composition is disclosed for reducing the extent of cardiac arrhythmias, both resulting from loss, decrease or interruption to the blood supply such as may happen during a heart attack or during cardiac surgery, in mammals. In particular, the present invention relates to a method of limiting or preventing cardiac cell damage and/or death, and limiting or preventing lethal or non-lethal cardiac arrhythmias, in a human, by administering to the cardiac cells a compound which selectively blocks or partially blocks persistent sodium currents and/or persistent sodium channels of cardiac cells. The composition involves any physiol. acceptable chemical or pharmaceutical composition comprising as its active ingredient a cardiac persistent sodium current and/or persistent sodium channel blocker.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:136851 HCAPLUS





TITLE: Recent advancea in anti-epileptic drugs
AUTHOR(S): Khan, S. A.; Lamba, H. S.; Rathour, Arvind; Budhwaar, Vikas; Pahwa, Rakesh; Manjusha
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, 110 062, India
SOURCE: Asian Journal of Chemistry (2007), 19(2), 823-835
CODEN: AJCHEW; ISSN: 0970-7077
PUBLISHER: Asian Journal of Chemistry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Epilepsies are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread. Some newer anti-epileptic drugs have recently been developed. They have some advantages over the older drugs. These newer drugs may control seizures more effectively. They are effective in complex partial and secondary generalized seizures. These are felbamate, vigabatrin, gabapetin, clobazam, lamotrigine, oxcarbazepine, tiagabine, topiramate, fosphenytoin, and zonisamide.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:61845 HCAPLUS
DOCUMENT NUMBER: 146:135588
TITLE: Neuroprotective carbamate deriva. for treatment of neurodegenerative disorders
INVENTOR(S): Zhao, Boyu; Tywman, Roy E.
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V., Belg.
SOURCE: PCT Int. Appl., 83pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007008562 | A2 | 20070118 | WO 2006-US26291 | 20060707 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| US 2007021500 | A1 | 20070125 | US 2006-481601 | 20060706 |

PRIORITY APPLN. INFO.: US 2005-698403P P 20050712
OTHER SOURCE(S): MARPAT 146:135588
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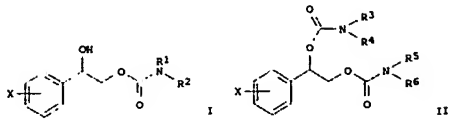

I II

AB This invention is directed to methods for providing neuroprotection comprising administering to a subject in need thereof a therapeutically effective amount of a compound selected from Formula (I) and Formula (II), where Ph is substituted at X with 1-5 halo atoms selected from F, C, B or I and R1-R6 = (un)substituted C1-C4 alkyl or pharmaceutical acceptable salts or esters thereof. Carbamate derivative decreased infarct volume following reperfusion in a rat model of transient cerebral ischemia arising from middle cerebral artery occlusion.

L16 ANSWER 5 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:61839 HCAPLUS
DOCUMENT NUMBER: 146:156257
TITLE: Carbamate compounds for treating epileptogenesis
INVENTOR(S): Tvyman, Roy E.; Zhao, Boyu
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V, Belg.
SOURCE: PCT Int. Appl., 82pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007008551 | A2 | 20070118 | WO 2006-US26277 | 20060707 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
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| US 2007021501 | A1 | 20070125 | US 2006-481626 | 20060706 |
| PRIORITY APPLN. INFO.: | | | US 2005-698625P | P 20050712 |
| OTHER SOURCE(S): | | | MARPAT 146:156257 | |

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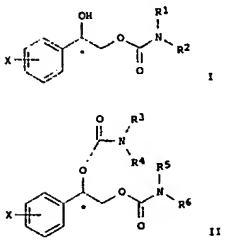


I II

AB The invention is directed to methods for preventing, treating, reversing, inhibiting, or arresting epileptogenesis in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound selected from the group consisting of Formula (I) and Formula (II)., where Ph is substituted at X with F, Cl, Br, or I; and R1-R6 = (un)substituted C1C4 alkyl or a pharmaceutically acceptable salt or ester thereof. A carbamate compound demonstrated anti-epileptogenic effects in rat model of spontaneous seizures.

L16 ANSWER 6 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1207236 HCAPLUS
DOCUMENT NUMBER: 145:495703
TITLE: Methods and compositions for the treatment of CNS-related conditions
INVENTOR(S): Went, Gregory T.; Pultz, Timothy J.
PATENT ASSIGNEE(S): Neurosolecular Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 58pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006121560 | A2 | 20061116 | WO 2006-US13506 | 20060406 |
| WO 2006121560 | A3 | 20070315 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, | | | | |





KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| US 2006142398 | A1 | 20060629 | US 2005-285905 | 20051122 |
| PRIORITY APPLN. INFO.: | | | US 2005-669290P | P 20050406 |
| | | | US 2005-285905 | A 20051122 |
| | | | US 2004-630885P | P 20041123 |
| | | | US 2004-635365P | P 20041210 |
| | | | US 2005-701857P | P 20050722 |

AB In general, the present invention provides methods and compns. for treating and preventing CNS-related conditions, such as neurodegenerative conditions (e.g., Alzheimer's disease and Parkinson's disease) and pain, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and a second agent such as acetylcholinesterase inhibitor (ACheI).

L16 ANSWER 7 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1173916 HCAPLUS
DOCUMENT NUMBER: 145:477933
TITLE: Methods and compositions for the treatment of CNS-related conditions
INVENTOR(S): Went, Gregory T.; Pultz, Timothy J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 29pp., Cont.-in-part of U.S. Ser. No. 285,905.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2006252786 | A1 | 20061109 | US 2006-399879 | 20060406 |
| US 2006142398 | A1 | 20060629 | US 2005-285905 | 20051122 |
| PRIORITY APPLN. INFO.: | | | US 2005-669290P | P 20050406 |
| | | | US 2005-285905 | A2 20051122 |
| | | | US 2004-630885P | P 20041123 |
| | | | US 2004-635365P | P 20041210 |
| | | | US 2005-701857P | P 20050722 |

AB The present invention provides novel methods and compns. for the treatment and prevention of CNS-related conditions. One of the CNS-related conditions treated by the methods and compns. of the invention is Alzheimer's disease.

L16 ANSWER 8 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:804735 HCAPLUS
DOCUMENT NUMBER: 146:243958
TITLE: Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings
AUTHOR(S): Clemens, Bela; Menes, Andrea; Piros, Palma; Bessenyei, Monika; Altmann, Anna; Jerney, Judit; Koller, Katalin; Rosdy, Beata; Rozsavoelgyi, Margit; Steinecker, Katalin; Hollody, Katalin
CORPORATE SOURCE: Epilepsy Center, Department of Neurology, Kenezy Gyula Memorial Hospital, Debrecen, 4031, Hung.
SOURCE: Epilepsy Research (2006), 70(2-3), 190-199
CODEN: EPIRE8; ISSN: 0920-1211
PUBLISHER: Elsevier Ltd.





DOCUMENT TYPE: Journal
LANGUAGE: English
AB Quant. EEG (QEEG) effects of therapeutic doses of carbamazepine (CBZ), oxcarbazepine (OXC), valproate (VA) and lamotrigine (LA) monotherapy were investigated in patients with beginning epilepsy. Baseline waking EEG (EEG1) was recorded in the untreated state, the second EEG (EEG2) was done after 8 wk of reaching the therapeutic dose. Left occipital data were used for anal. QEEG target parameters were absolute band-power (delta: AD, theta: AT, alpha: AA, beta: AB), and alpha mean frequency (AMF). Group effects (untreated vs. treated condition in the CBZ, VA, OXC, LA groups) were computed for each target parameter. One group with benign rolandic epilepsy remained untreated for clin. reasons and served to estimate the QEEG test-retest differences. In addition, the individual QEEG response to each drug was calculated as (EEG2 - EEG1). Results: statistically significant ($p < 0.05$) group differences indicated the QEEG domain systematically affected by the drugs. CBZ caused AT increase and AMF decrease. OXC caused AMF decrease. VA and LA did not decrease AMF (LA even increased it), but reduced broad-band power. Individual power and AMF changes showed considerable variability in each group. >0.5 Hz AMF decrease (that was reported to predict cognitive impairment in prior studies) occurred in 10/41 patients in the CBZ group but never in the OXC, VA, LA groups. The results may be utilized in planning further studies addressing the relationship between antiepileptic drugs and their CNS effects. In addition, the relationship of AED-related cognitive impairment and AMF changes was discussed.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:740619 HCAPLUS
DOCUMENT NUMBER: 145:159852
TITLE: Method for treating borderline personality disorder and self-injurious behavior with glutamate-modulating agents
INVENTOR(S): Feuerstein, Seth; Coric, Vladimir
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2006167068 | A1 | 20060727 | US 2006-339881 | 20060126 |
| PRIORITY APPLN. INFO.: | | | US 2005-647535P | P 20050126 |

AB Glutamate-modulating agents are useful for treating borderline personality disorder and self-injurious behavior. Methods for treating borderline personality and self-injurious behavior are provided which involve administering a glutamate-modulating agent to a patient. The invention also includes combination methods of treatment in which a glutamate-modulating agent is administered with one or more other CNS active agents. Packaged pharmaceutical compns. containing a glutamate-modulating agent and one or more other CNS agent are also provided, as are packaged pharmaceutical formulations containing a glutamate-modulating agent and instructions for using the glutamate-modulating agent for treating borderline personality disorder or self-mutilating behavior.

L16 ANSWER 10 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:493860 HCAPLUS
DOCUMENT NUMBER: 144:481072
TITLE: Methods and compositions for treating pain
INVENTOR(S): Robbins, Wendye
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 61 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2006111307 | A1 | 20060525 | US 2005-281791 | 20051116 |
| US 2006111308 | A1 | 20060525 | US 2005-281984 | 20051116 |
| WO 2006055672 | A2 | 20060526 | WO 2005-US41608 | 20051116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| GB 2423928 | A | 20060913 | GB 2006-6028 | 20051116 |
| PRIORITY APPLN. INFO.: | | | US 2004-628646P | P 20041116 |
| | | | WO 2005-US41608 | W 20051116 |

AB Methods and compns. are described for the modulation of central nervous system and/or fetal effects of substances. Methods and compns. are described for the modulation of efflux transporter activity to increase the efflux of drugs and other compds. out of a physiol. compartment and into an external environment. In particular, the methods and compns. disclosed herein provide for the increase of efflux transporter activity at blood-brain, blood-CSF and placental-maternal barriers to increase the efflux of drugs and other compds. from physiol. compartments, including central nervous system and fetal compartments.

L16 ANSWER 11 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:383992 HCAPLUS
DOCUMENT NUMBER: 144:404414
TITLE: Carbamate compounds for use in treating neurodegenerative disorders
INVENTOR(S): Twyman, Roy E.; Zhao, Boyu
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V., Belg.
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

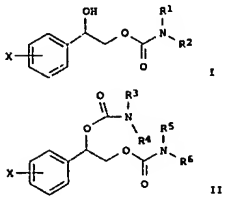
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|





| | | | | |
|---|---|---|---|---|
| WO 2006044472 | A1 | 20060427 | WO 2005-US36695 | 20051014 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| PRIORITY APPLN. INFO.: | | | US 2004-619402P | P 20041015 |
| | | | US 2005-698403P | P 20050712 |

OTHER SOURCE(S): MARPAT 144:404414
GI



I



II

AB The invention discloses methods for providing neuroprotection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound I or II [Ph is substituted at X with 1-5 halo atoms selected from F, Cl, Br, I; R1-R6 = H, (un)substituted C1-C4 alkyl], or a pharmaceutically acceptable salt or ester thereof.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 12 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:333530 HCAPLUS
DOCUMENT NUMBER: 144:324867
TITLE: Methods of treating epileptogenesis and epilepsy
INVENTOR(S): Choi, Yong Moon; Gordon, Robert; Novsk, Gerald P.; Plats-Salaman, Carlos R.; Twyman, Roy E.; White, H. Steve; Zhao, Boyu
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V., Belg.
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent





LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006033947 | A2 | 20060330 | WO 2005-US32861 | 20050915 |
| WO 2006033947 | A3 | 20060629 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 2006194873 | A1 | 20060831 | US 2005-227247 | 20050915 |
| PRIORITY APPLN. INFO.: | | | US 2004-610276P | P 20040916 |
| | | | US 2005-698625P | P 20050712 |
| | | | US 2005-707242P | P 20050811 |

OTHER SOURCE(S): MARPAT 144:324867
AB This invention is directed to methods for preventing, treating, reversing, inhibiting or arresting epilepsy and epileptogenesis in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound selected from the group consisting of Formula (I) and Formula (II), or a pharmaceutically acceptable salt or ester thereof,: Formula (I) Formula (II) wherein Ph is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and, R1, R2, R3, R4, R5 and R6 are independently selected from the group consisting of hydrogen and C1-C4 alkyl; wherein C1-C4 alkyl is optionally substituted with Ph (wherein Ph is optionally substituted with substituents independently selected from the group consisting of halogen, C1-C4 alkyl, C1-C4 alkoxy, amino, nitro and cyano).

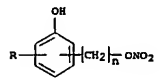
L16 ANSWER 13 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:149768 HCAPLUS
DOCUMENT NUMBER: 144:232798
TITLE: Preparation of nitroxyalkyl derivatives of phenol for treating inflammatory, cardiovascular and peripheral vascular diseases
INVENTOR(S): Ongini, Ennio; Impagnatiello, Francesco
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006015930 | A1 | 20060216 | WO 2005-EP53500 | 20050720 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, | | | | |





GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2004-599857P P 20040810
OTHER SOURCE(S): MARPAT 144:232798
GI



I

AB The title compds. I [n = 1-20; R = H, halo, a linear or branched (C1-C10)alkoxy, OH, CF3, NHR' (wherein R' = H or a linear or branched (C1-C10)alkyl); or a salt thereof], useful for treating inflammatory disease states or disorders, cardiovascular and/or peripheral vascular diseases, were prepared E.g., a benzenemethanol, 3-hydroxy-α-nitrate (II) was prepared from com. available 3-[(hydroxy)methyl]phenol using 2-step process. Effects of II on inflammatory markers were tested. For example, the compound II applied alone or in combination with ASA inhibited LPS/INFγ-induced nitrites accumulation with similar potency as that estimated for NCX 4016 (EC50 = 58 μM and 57 μM, resp. for compound II alone and in combination with ASA). The pharmaceutical compns. comprising the compound II alone or in combination with other therapeutic agents are disclosed.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 14 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:149494 HCAPLUS
DOCUMENT NUMBER: 144:205795
TITLE: Preventing pathological increases in the rate of nerve cell suicide in immature nervous systems
INVENTOR(S): Olney, John W.
PATENT ASSIGNEE(S): Olney, John, W., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006017524 | A2 | 20060216 | WO 2005-US27460 | 20050802 |
| WO 2006017524 | A3 | 20060831 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, | | | | |

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-598390P P 20040802

AB Methods and compds. are disclosed for reducing brain damage in fetuses, neonates, and young infants, caused by surgical anesthetics. During critical periods of synapse formation and network development in the brain, CNS neurons that do not appear to be keeping pace with certain synchronized development and connection processes are regarded as surplus, and are destroyed by a programmed cell suicide process called apoptosis. As a result, if surgical anesthetics block neuronal responses and activities that normally would indicate that a certain CNS neuron is indeed active and involved in a network and should be preserved, such anesthesia can induce apoptotic death, in the unreasonable anesthetized neurons. That process, which can cause permanent brain damage, can be minimized by manipulating certain signaling pathways that affect the balance between apoptosis-promoting proteins ( e.g., Bax and Bak) and apoptosis-blocking proteins ( e.g., Bcl-2 and Bcl-xL). Agents that have been tested and shown to reduce anesthesia-induced brain damage in neonatal animals include xenon (which promotes ERK MAPKinase activity), and muscarinic cholinergic agonists (which can promote ERK MAPKinase, PKA, PKC, and/or PI3K/AKT activity). Other candidate agents with similar activities include lithium, beta-1 adrenergic antagonists, and beta-2 adrenergic agonists. Such agents must intervene in the "upstream" part of the apoptosis cascade, before mitochondrial membranes become permeable and begin to release "cytochrome c" messenger mols.

L16 ANSWER 15 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:962027 HCAPLUS
DOCUMENT NUMBER: 143:235530
TITLE: Methods and compositions for the treatment of epilepsy, seizure disorders, and other CNS disorders
INVENTOR(S): Went, Gregory; Fultz, Timothy J.; Meyerson, Lawrence
PATENT ASSIGNEE(S): Neuromolecular, Inc., USA; Neuromolecular Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005079773 | A2 | 20050901 | WO 2005-US4819 | 20050214 |
| WO 2005079773 | A3 | 20051027 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, | | | | |





NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

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|---|---|---|---|---|
| AU 2005215767 | A1 | 20050901 | AU 2005-215767 | 20050214 |
| CA 2556214 | A1 | 20050901 | CA 2005-2556214 | 20050214 |
| EP 1727538 | A2 | 20061206 | EP 2005-732251 | 20050214 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR | | | | |
| CN 1929830 | A | 20070314 | CN 2005-80007919 | 20050214 |

PRIORITY APPLN. INFO.:
US 2004-544839P P 20040213
US 2004-603903P P 20040824
US 2004-635786P P 20041213
WO 2005-US4819 W 20050214

AB The present invention relates to compns. comprising an NMDA receptor antagonists and an anti-epileptic drug for the treatment of CNS -related disorders. For example, tablets were formulated containing memantine 10, topiramate 30, dicalcium phosphate dihydrate 26.6, microcryst. cellulose 26.6, Na starch glycolate 1.2, Mg stearate 0.6, Eudragit RS30D 4.76, talc 3.3, and tri-Et citrate 0.95 mg per tablet.

L16 ANSWER 16 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:673292 HCAPLUS
DOCUMENT NUMBER: 143:172866
TITLE: Preparation of isothiazole dioxides as CXC- and CC-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Zheng, Junying; Biju, Purakkattle J.; Yu, Younong; Chao, Jianhua; Fine, Jay; Lundell, Daniel; Priestley, Tony; Reggiani, Angelo; Merritt, J. Robert; Baldwin, John J.; Lai, Gaifa; Wu, Minglang
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 427 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005068460 | A1 | 20050728 | WO 2004-US42720 | 20041220 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2550540 | A1 | 20050728 | CA 2004-2550540 | 20041220 |
| US 2006025453 | A1 | 20060202 | US 2004-17505 | 20041220 |
| EP 1697354 | A1 | 20060906 | EP 2004-814856 | 20041220 |





R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU

| | | | | |
|---|---|---|---|---|
| CN 1918156 | A | 20070221 | CN 2004-80041794 | 20041220 |

PRIORITY APPLN. INFO.:
US 2003-531693P P 20031222
WO 2004-US42720 W 20041220

OTHER SOURCE(S): MARPAT 143:172866
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed are novel compds. I [D, E = N, CR50; provided that D and E are not the same (one is N and the other is CR50); R50 = H, CF3, CN, etc.; A = (hetero)aryl, (hetero)arylalkyl; B = (hetero)aryl] and the pharmaceutically acceptable salts and solvates thereof. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, pain (e.g., acute pain, acute and chronic inflammatory pain, and neuropathic pain) using a compound I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 68% yield from the isothiazoledioxide III and the amine IV.pTSA (preparation of reactants given). Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 17 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:638859 HCAPLUS
DOCUMENT NUMBER: 143:153384
TITLE: Preparation of diaminothiadiazoles as CXC- and CC-chemokine receptor ligands
INVENTOR(S): Biju, Purakkattle J.; Taveras, Arthur G.; Yu, Younong; Zheng, Junying; Chao, Jianhua; Aki, Cynthia J.; Fine, Jay; Lundell, Daniel; Priestley, Tony; Reggiani, Angelo; Merritt, J. Robert; Baldwin, John J.
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 593 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005066147 | A1 | 20050721 | WO 2004-US42060 | 20041216 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, | | | | |





AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| CA 2550189 | A1 | 20050721 | CA 2004-2550189 | 20041216 |
| EP 1694659 | A1 | 20060830 | EP 2004-814266 | 20041216 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU | | | | |
| US 2006223864 | A1 | 20061005 | US 2004-13753 | 20041216 |
| CN 1918138 | A | 20070221 | CN 2004-80041695 | 20041216 |

PRIORITY APPLN. INFO.:
US 2003-531311P P 20031219
US 2003-531713P P 20031222
WO 2004-US42060 W 20041216

OTHER SOURCE(S): MARPAT 143:153384
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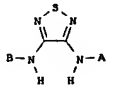
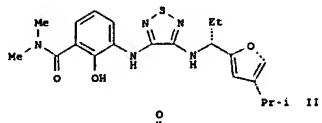
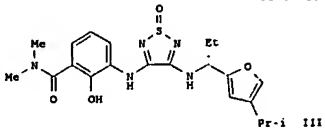




Pr-i II



Pr-i III

AB Disclosed are diaminothiadiazoles I [A = (hetero)aryl, (hetero)arylmethyl (substituted at CH2), etc.; B = (hetero)aryl] and the pharmaceutically acceptable salts and solvates thereof. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and ischemia reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 43% yield from its monooxide III (preparation given). Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7

are given.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 18 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:364521 HCAPLUS
DOCUMENT NUMBER: 143:126473
TITLE: Valproic acid, but not lamotrigine, suppresses seizure-induced c-fos and c-Jun mRNA expression
AUTHOR(S): Szot, Patricia; White, Sylvia S.; Shen, Danny D.; Anderson, Gail D.
CORPORATE SOURCE: Mental Illness Research Education and Clinical Center (MIRECC), VA Puget Sound Health Care System, Seattle, WA, 98108, USA
SOURCE: Molecular Brain Research (2005), 135(1-2), 285-289
CODEN: MBREE4; ISSN: 0169-328X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Seizure-induced activity was shown to increase the expression of immediate early genes (IEGs) c-fos and c-Jun in the CNS. Antiepileptic drugs (AEDs) can suppress the induction of a seizure, but it is unknown if AEDs affect the expression of seizure-induced IEGs. The authors found that valproic acid (VPA), but not lamotrigine (LTG), was capable of suppressing seizure-induced c-fos and c-Jun mRNA expression in rats despite a similar anticonvulsant effect. LTG in some regions of the CNS enhanced seizure-induced IEG expression. These studies indicate that the older AED (VPA), as compared to the newer AED (LTG), can suppress seizure-induced IEG expression. The consequence of this suppression of IEGs following a generalized seizure may be viewed either as a neuroprotective or detrimental effect upon the brain.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 19 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:288391 HCAPLUS
DOCUMENT NUMBER: 143:71550
TITLE: Adverse reactions of topiramate and lamotrigine in children
AUTHOR(S): Shechter, Tamar; Shorer, Zamir; Kramer, Uri; Lerman-Sagie, Tally; Ronen, Eliaheva; Rotem, Rimona; Gorodischer, Rafael
CORPORATE SOURCE: Pharmacy Services, Soroka Medical Center, Be'er Sheva, Israel
SOURCE: Pharmacoepidemiology and Drug Safety (2005), 14(3), 187-192
CODEN: PDSAEA; ISSN: 1053-8569
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: To review the adverse drug reactions (ADRs) of Topiramate and Lamotrigine among children in Israel, and to compare the two drugs, based on their side effect profile and tolerability among this population. Methods: We performed a cross-sectional study. Four pediatric neurologists from three different tertiary medical centers in Israel documented all cases of children from birth to the age 18 years, treated with Topiramate and/or Lamotrigine in their resp. outpatient clinics and hospital wards. All present ADRs and their characteristics were recorded. Results: Reports on 45 and 65 children treated with Topiramate and





Lamotrigine resp., were received. Half of the children treated with Topiramate suffered from one or more ADRs, as opposed to one-third of the children treated with Lamotrigine ($p = 0.03$). Most reactions were considered mild to moderate. There were no deaths or hospitalizations, but the drug had to be discontinued in about 10% of the patients due to ADRs. Most Topiramate and Lamotrigine ADRs appeared early in the treatment and were more frequent when Topiramate was an add-on vs. a monotherapy drug. Most ADRs of both Topiramate and Lamotrigine were related to the central nervous system; while poor appetite, drowsiness, speech difficulties and weight loss were observed only with Topiramate, and rash and headaches only with Lamotrigine. Nervousness and seizure aggravation were more frequent ADRs of Topiramate whereas sleep disturbances were observed more in children treated with Lamotrigine. Conclusion: Results of this study indicate that Lamotrigine causes ADRs less frequently than Topiramate; however both medications are generally well tolerated. Topiramate and Lamotrigine differ in their central nervous system side effect profile.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 20 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:53146 HCAPLUS
DOCUMENT NUMBER: 142:290582
TITLE: Relationship between exposure and nonspecific binding of thirty-three central nervous system drugs in mice
AUTHOR(S): Maurer, Tristan S.; DeBartolo, Demetria B.; Tess, David A.; Scott, Dennis O.
CORPORATE SOURCE: Pharmacokinetics, Pharmacodynamics and Drug Metabolism, Pfizer Global Research and Development, Groton Laboratories, Groton, CT, USA
SOURCE: Drug Metabolism and Disposition (2005), 33(1), 175-181
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unbound fractions in mouse brain and plasma were determined for 31 structurally diverse central nervous system (CNS) drugs and two active metabolites. Three comparisons were made between in vitro binding and in vivo exposure data, namely: (1) mouse brain-to-plasma exposure vs. unbound plasma-to-unbound brain fraction ratio (fuplasma/fubrain), (2) cerebrospinal fluid-to-brain exposure vs. unbound brain fraction (fubrain), and (3) cerebrospinal fluid-to-plasma exposure vs. unbound plasma fraction (fuplasma). Unbound fraction data were within 3-fold of in vivo exposure ratios for the majority of the drugs examined (i.e., 22 of 33), indicating a predominately free equilibrium across the blood-brain and blood-CSF barriers. Some degree of distributional impairment at either the blood-CSF or the blood-brain barrier was indicated for 8 of the 11 remaining drugs (i.e., carbamazepine, midazolam, phenytoin, sulpiride, thiopental, risperidone, 9-hydroxyrisperidone, and zolpidem). In several cases, the indicated distributional impairment is consistent with other independent literature reports for these drugs. Through the use of this approach, it appears that most CNS-active agents freely equilibrate across the blood-brain and blood-CSF barriers such that unbound drug concns. in brain approx. those in the plasma. However, these results also support the intuitive concept that distributional impairment does not necessarily preclude CNS activity.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS





RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 21 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:53345 HCAPLUS
DOCUMENT NUMBER: 142:290581
TITLE: The impact of P-glycoprotein on the disposition of drugs targeted for indications of the central nervous system: Evaluation using the MDR1A/1B knockout mouse model
AUTHOR(S): Doran, Angela; Obach, R. Scott; Smith, Bill J.; Hosea, Natilie A.; Becker, Stacey; Callegari, Ernesto; Chen, Cuiping; Chen, Xi; Choo, Edna; Cianfrogna, Julie; Cox, Loretta M.; Gibbs, John P.; Gibbs, Megan A.; Hatch, Heather; Hop, Cornelia E. C. A.; Kasman, Ilana N.; LaPerle, Jennifer; Liu, JianHua; Liu, Xingrong; Logman, Michael; Maclin, Debra; Nedza, Frank M.; Nelson, Frederick; Olson, Emily; Rahematpura, Sandhya; Raunig, David; Rogers, Sabrinia; Schmidt, Kari; Spracklin, Douglas K.; Szawc, Mark; Troutman, Matthew; Tseng, Elaine; Tu, Meihua; Van Deusen, Jeffrey W.; Venkatakrishnan, Karthik; Walena, Gary; Wang, Ellen Q.; Wong, Diana; Yaagar, Adam S.; Zhang, Chenghong
CORPORATE SOURCE: Departments of Pharmacokinetics, Dynamics, and Drug Metabolism, Pfizer Global Research and Development, Groton Laboratories, Groton, CT, USA
SOURCE: Drug Metabolism and Disposition (2005), 33(1), 165-174
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thirty-two structurally diverse drugs used for the treatment of various conditions of the central nervous system (CNS), along with two active metabolites, and eight non-CNS drugs were measured in brain, plasma, and cerebrospinal fluid in the P-glycoprotein (P-gp) knockout mouse model after s.c. administration, and the data were compared with corresponding data obtained in wild-type mice. Total brain-to-plasma (B/P) ratios for the CNS agents ranged from 0.060 to 24. Of the 34 CNS-active agents, only 7 demonstrated B/P area under the plasma concentration curve ratios between P-gp knockout and wild-type mice that did not differ significantly from unity. Most of the remaining drugs demonstrated 1.1- to 2.6-fold greater B/P ratios in P-gp knockout mice vs. wild-type mice. Three, risperidone, its active metabolite 9-hydroxyrisperidone, and metoclopramide, showed marked differences in B/P ratios between knockout and wild-type mice (6.6- to 17-fold). Differences in B/P ratios and cerebrospinal fluid/plasma ratios between wild-type and knockout animals were correlated. Through the use of this model, it appears that most CNS-active agents demonstrate at least some P-gp-mediated transport that can affect brain concns. However, the impact for the majority of agents is probably minor. The example of risperidone illustrates that even good P-gp substrates can still be clin. useful CNS-active agents. However, for such agents, unbound plasma concns. may need to be greater than values projected using receptor affinity data to achieve adequate receptor occupancy for effect.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 22 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:927018 HCAPLUS





DOCUMENT NUMBER: 141:388733
TITLE: Compositions of a cyclooxygenase-2 selective inhibitor and a sodium ion channel blocker for the treatment of central nervous system damage
INVENTOR(S): Stephenson, Diane T.; Taylor, Duncan P.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004093811 | A2 | 20041104 | WO 2004-US12383 | 20040421 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004224940 | A1 | 20041111 | US 2004-829009 | 20040421 |
| PRIORITY APPLN. INFO.: | | | US 2003-464499P P | 20030422 |
| | | | US 2003-464830P P | 20030423 |

OTHER SOURCE(S): MARPAT 141:388733
AB The invention provides compns. and methods for the treatment of central nervous system damage in a subject. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic condition or a central nervous system traumatic injury comprising the administration to a subject of a sodium ion channel blocker in combination with a cyclooxygenase-2 selective inhibitor. Uses for the treatment of stroke is specifically claimed.

L16 ANSWER 23 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:802560 HCAPLUS
DOCUMENT NUMBER: 141:301459
TITLE: Novel formulations and method of treatment
INVENTOR(S): Buxton, Ian Richard; Currie, Robin; Dela-Cruz, Myrna A.; Goodson, Gary Wayne; Karolak, Wlodzimierz; Maleki, Mehran; Iyer, Vijay Mohan; Gopal, Muppirala; Parr, Alan Frank; Sidhu, Jagdev Singh; Stagner, Robert Allen; Vijay-Kumar, Akunuri Venkata
PATENT ASSIGNEE(S): Can.
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 629,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| US 2004192690 | A1 | 20040930 | US 2003-726752 | | 20031204 |
| US 2005032799 | A1 | 20050210 | US 2003-629177 | | 20030729 |
| PRIORITY APPLN. INFO.: | | | GB 2002-17492 | A | 20020729 |
| | | | GB 2002-17493 | A | 20020729 |
| | | | GB 2003-13801 | A | 20030613 |
| | | | US 2003-629177 | A2 | 20030729 |

AB A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof and methods of treatment and uses thereof are disclosed.

L16 ANSWER 24 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:740119 HCAPLUS
DOCUMENT NUMBER: 141:254587
TITLE: Methods and compositions for the treatment of chronic pain using dehydroepiandrosterone (DHEA) and derivatives thereof, alone or in combination with another drug
INVENTOR(S): Lucas, John M.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004075832 | A2 | 20040910 | WO 2004-US4861 | 20040219 |
| WO 2004075832 | A3 | 20050324 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2006178354 | A1 | 20060810 | US 2005-546882 | 20050826 |
| PRIORITY APPLN. INFO.: | | | US 2003-450271P | P 20030227 |
| | | | WO 2004-US4861 | W 20040219 |

AB The invention relates to the treatment of chronic pain using DHEA or derivs. thereof either alone or in combination with at least one other drug. The invention also includes compns. compriaing DHEA or a derivative thereof and a second drug.

L16 ANSWER 25 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:120727 HCAPLUS
DOCUMENT NUMBER: 140:169680
TITLE: Sustained release formulations comprising lamotrigine
INVENTOR(S): Buxton, Ian Richard; Currie, Robin; Dela-Cruz, Myrna A.; Goodson, Gary Wayne; Karolak, Wlodzimierz; Maleki, Mehran; Iyer, Vijay Mohan; Muppirala, Gopal; Parr, Alan Frank; Sidhu, Jagdev Singh; Stagner, Robert Allen; Vijay-kumar, Akunuri Venkata
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; et al.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent





LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004012741 | A1 | 20040212 | WO 2003-EP8368 | 20030728 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2493301 | A1 | 20040212 | CA 2003-2493301 | 20030728 |
| AU 2003260336 | A1 | 20040223 | AU 2003-260336 | 20030728 |
| EP 1524981 | A1 | 20050427 | EP 2003-766343 | 20030728 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003013148 | A | 20050712 | BR 2003-13148 | 20030728 |
| CN 1681509 | A | 20051012 | CN 2003-822371 | 20030728 |
| JP 2005538113 | T | 20051215 | JP 2004-525362 | 20030728 |
| NO 2005000948 | A | 20050222 | NO 2005-948 | 20050222 |
| PRIORITY APPLN. INFO.: | | | GB 2002-17492 | A 20020729 |
| | | | GB 2002-17493 | A 20020729 |
| | | | GB 2003-13801 | A 20030613 |
| | | | WO 2003-EP8368 | W 20030728 |

AB A sustained-release formulation, especially tablet, of lamotrigine or its derivative
for treatment of CNS disorder comprises (by weight) 2.5 to 80% lamotrigine or its derivative, 10 to 70% releaae retarding polymer, 0 to 70% diluent, 0 to 20% compreaaion aid, and 0.1 to 2.5% lubricant. Substantially all the lamotrigine or a pharmaceutically acceptable derivative is releaaed from the formulation in a period of 2 to 20 h after administration to a patient, producing an Area Under the Curve value of 80 to 125% and Cmax of about 30% less than that of an inatant-release tablet containing the same amount of lamotrigine. For example, a tablet formulation (Diffcore device) was prepared comprising (i) a core containing lamotrigine 200 mg, a blend of hydroxypropyl Me celluloses K100LV 62.64 mg and K4M 45.36 mg, lactose monohydrate 90.4 mg, and magneaium stearate 1.6 mg, and (ii) an outer coat containing Eudragit L30 D-55 (30% weight/weight solution) 17.3 mg, Red Iron Oxide 0.37 mg, tri-Et citrate 1.81 mg, glyceryl monostearate 0.494 mg, and Polysorbate 80 0.02 mg. The coating included orifices allowing the release of lamotrigine from the core.

L16 ANSWER 26 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:61937 HCAPLUS
DOCUMENT NUMBER: 141:342
TITLE: Brain access and anticonvulsant efficacy of carbamazepine, lamotrigine, and felbamate in ABCC2/MRP2-deficient TR- rats
AUTHOR(S): Potschka, Heidrun; Fedrowitz, Maren; Loescher, Wolfgang
CORPORATE SOURCE: Department of Pharmacology, Toxicology, and Pharmacy, School of Veterinary Medicine, Hannover, Germany





SOURCE: Epilepsia (2003), 44(12), 1479-1486
CODEN: EPILAK; ISSN: 0013-9580
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Different ATP (ATP)driven multidrug transporters have been described to be expressed in the luminal membrane of blood-brain barrier (BBB) endothelial cells. At this site, multidrug transporters have been suggeated to restrict penetration of drugs into the brain. Increasing evidence suggests that overexpreaaion of different multidrug transporters occurs in the region of the epileptic focus of pharmacoresistant epilepsy patients. Based on the assumption that antiepileptic drugs (AEDs) are subatrates of these transporters, this overexpression may limit access of AEDs to epileptic neurons and may contribute to drug-refractoriness. In a recent study, overexpression of multidrug resistance protein 2 (ABCC2; MRP2) was reported in BBB endothelial cells of epileptic focal tissue from pharmacoresistant patients. With brain microdialyais, we recently demonstrated that the AED phenytoin is subject to transport by ABCC2 at the BBB, whereas phenobarbital does not seem to be a substrate of ABCC2. We investigated whether ABCC2 is functionally involved in tranaport of the AEDs carbamazepine (CBZ), lamotrigine (LTG), and felbamate (FBM) across the BBB. The distribution of these AEDs into the brain of ABCC2-deficient TR- rats was determined AED concns. in plasma and brain extracellular space of these mutant rats did not differ significantly from those of rats of the corresponding background strain. In the amygdalakindling model of epilepsy, the anticonvulsant efficacy of LTG and FBM was comparable in both groups of rats. In contrast, CBZ exhibited a higher anticonvulsant activity in kindled ABCC2-deficient rats as compared with nonmutant rats. In this present study, the microdialysis results gave no evidence that ABCC2 function modulates entry of CBZ, LTG, and FBM into the CNS of naive rats. However, ABCC2 deficiency was associated with an increased anticonvulsant response of CBZ in the kindling model. Future investigations are planned to identify the underlying mechanism for this difference, clarifying whether a pharmacokinetic difference is detectable only when brain access of CBZ is compared in kindled ABCC2-deficient rats and kindled nonmutant rats, which may have an increased expression of ABCC2 in response to seizures. The data substantiate that ABCC2-deficient TR- rats are a useful tool for defining the role of ABCC2 for transport of AEDs, and give evidence that the use of kindled TR- rats may provide important supplementary information.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 27 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:962301 HCAPLUS
DOCUMENT NUMBER: 141:1649
TITLE: Glutamate-dependent regulation of cholinergic phenotype in hypothalamic neurons
AUTHOR(S): Belousov, Andrei B.
CORPORATE SOURCE: Department of Cell and Molecular Biology, Tulane University, New Orleans, LA, 70118, USA
SOURCE: NeuroReport (2003), 14(18), 2445-2449
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamate NMDA receptor antagonists are used clin. However, they have serious side effects, some of which are presumably due to an increase in acetylcholine transmission. The authors' previous expts. revealed





acetylcholine-dependent excitation in rat hypothalamic culturea after a chronic glutamate receptor blockade. Dextromethorphan, amantadine, and eliprodil are NMDA receptor antagoniata. Lamotrigine inhibits synaptic glutamate releaae. These drugs are used clin. Here, using calcium imaging and immunocytochem., the authors demonstrate that a chronic treatment with each of these drugs induced acetylcholine activity and choline acetyltransferaae immunoreactivity in rat hypothalamic (but not cortical) cultures. Theae data support the possibility that some side effects of anti-glutamate drugs in vivo may be due to the increase in cholinergic properties in certain regions of the CNS.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 28 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:769633 HCAPLUS
DOCUMENT NUMBER: 140:263619
TITLE: Relationship between lamotrigine oral dose, serum level and its inhibitory effect on CNS: insights from tranacranial magnetic stimulation
AUTHOR(S): Tergau, Frithjof; Wischer, Stephan; Somal, Hardyal S.; Nitsche, Michael A.; Mercer, A. Joe; Paulua, Walter; Steinhoff, Bernhard J.
CORPORATE SOURCE: Department of Clinical Neurophysiology, University of Gottingen, Gottingen, D-37075, Germany
SOURCE: Epilepsy Research (2003), 56(1), 67-77
CODEN: EPIRES; ISSN: 0920-1211
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antiepileptic drug lamotrigine (LTG) is known to reduce cortical excitability evaluated by transcranial magnetic stimulation (TMS). We investigated the relationship between LTG oral dosages, serum levels and inhibitory effects on resting motor threshold (RMT), a parameter of motor system excitability aaaeaaed by TMS. In a randomized, placebo-controlled crossover study 16 male volunteers received 325 mg LTG as a single dose, as bi-hourly graded cumulative dose, or placebo. RMT and serum levels were meaaured before and after 2-8 h. With single doae, RMT elevation showed a poor but significant correlation to serum levels. With graded dose, serum levels as well as RMT increaaed dose-dependently with significant (P<0.0001) linear correlation. However, detailed comparison showed a high inter-individual variability in the relationship resembling a aigmoid correlation. Different mechanisms beaidea the sodium-channel blockage as the main mode of action of LTG are diacuaaed to explain the diversity of individual dose-reaponse relationshipa. Provided that the RMT elevation reflecta the antiepileptic potential of LTG, TMS may be developed aa a tool to monitor interindividual response of epilepsy patienta to LTG treatment as well aa to explore efficacy of other antiepileptic drugs with similar mode of action.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 29 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:376842 HCAPLUS
DOCUMENT NUMBER: 138:385297
TITLE: Methods for treating depression and other CNS disorders using enantiomerically enriched desmethyl- and didesmethyl- metabolites of citalopram
INVENTOR(S): Bush, Larry R.; Currie, Mark G.; Senanayake, Chris H.; Fang, Kevin Q.

PATENT ASSIGNEE(S): Sepracor, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003040121 | A1 | 20030515 | WO 2002-US35408 | 20021105 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2465186 | A1 | 20030515 | CA 2002-2465186 | 20021105 |
| AU 2002356903 | A2 | 20030519 | AU 2002-356903 | 20021105 |
| EP 1446396 | A1 | 20040818 | EP 2002-802848 | 20021105 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| BR 2002013949 | A | 20040831 | BR 2002-13949 | 20021105 |
| HU 200401934 | A2 | 20050128 | HU 2004-1934 | 20021105 |
| JP 2005510518 | T | 20050421 | JP 2003-542167 | 20021105 |
| CN 1705654 | A | 20051207 | CN 2002-822084 | 20021105 |
| IN 2004KN00505 | A | 20060616 | IN 2004-KN505 | 20040419 |
| ZA 2004003409 | A | 20051026 | ZA 2004-3409 | 20040505 |
| US 2004266864 | A1 | 20041230 | US 2004-842055 | 20040507 |
| NO 2004002013 | A | 20040514 | NO 2004-2013 | 20040514 |
| PRIORITY APPLN. INFO.: | | | US 2001-337608P P | 20011108 |
| | | | WO 2002-US35408 W | 20021105 |

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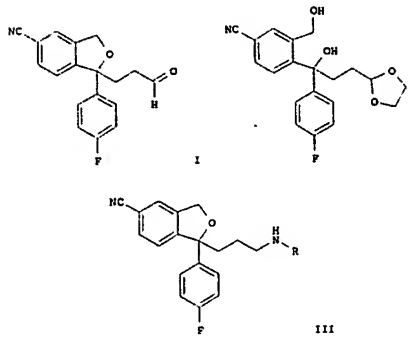



AB This invention relates to the preparation of I and II and derivs. of I and II in their racemic, enantiomerically enriched, or optically pure forms. This invention further relates to novel compns. of matter containing enantiomerically enriched (-)-desmethylcitalopram (-)-III (R = Me), (+)-didesmethylcitalopram (+)-III (R = Me), or (-)-didesmethylcitalopram (-)-III (R = H) or mixts. thereof in optimal ratios. Contrary to prior teachings, the enantiomerically enriched citalopram metabolites disclosed herein possess potent serotonin reuptake inhibitory activity, with minimal inhibitory effects on the reuptake of other known monoamines, e.g., norepinephrine (NE) or dopamine (DA). For example, stepwise reaction of 1-oxo-1,3-dihydroisobenzofuran-5-carbonitrile with 4-fluorophenylmagnesium bromide and the chiral Grignard reagent, which was prepared from 2-(2-bromoethyl)-[1,3]dioxolane and Mg powder, in THF gave II. Cyclization using mesyl chloride in CH2Cl2, followed by reduction provided the I. Reaction of the aldehyde with (-)-tert-butylsulfinamide in the presence of Ti(OEt)4 in EtOH afforded the sulfinamide, which was reduced to the amine III (R = H) with 10% HCl in MeOH. Protection of the amine with BOC anhydride in the presence of TEA in CH2Cl2 provided the enantiomerically enriched isomers, which were separated on a chiral column and subsequently deprotected with TFA to give (+)-III (R = H) and (-)-III (R = H). In biol. assays, (-)-III (R = H) and (+)-III (R = H) strongly inhibited serotonergic 5-HT receptor activity with Ki values of 5.8 nM and 90 nM, resp., with little effect on NE and DA transporter activity. By comparison, racemic citalopram inhibited serotonin reuptake with a Ki of 3.9 nM. The present invention also discloses methods for treating disorders, dysfunctions and diseases for which inhibition of serotonin reuptake is therapeutically beneficial. In particular, the present invention discloses a method for treating various forms of depression and other CNS disorders with pharmaceutical compns. described herein.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS





RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 30 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:319348 HCAPLUS
DOCUMENT NUMBER: 138:331688
TITLE: Methods of suppressing microglial activation and systemic inflammatory responses
INVENTOR(S): Laskowitz, Daniel T.; Matthew, William D.; McMillian, Michael
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 48 pp., Cont.-in-part of U.S. Ser. No. 957,909.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003077641 | A1 | 20030424 | US 2002-252120 | 20020923 |
| US 2002164789 | A1 | 20021107 | US 2001-957909 | 20010921 |
| PRIORITY APPLN. INFO.: | | | US 1998-77551P P | 19980311 |
| | | | US 1999-260430 B2 | 19990301 |
| | | | US 2001-957909 A2 | 20010921 |

AB Methods of suppressing the activation of microglial cells in the Central Nervous System (CNS), methods of ameliorating or treating the neurol. effects of cerebral ischemia or cerebral inflammation, and methods of combating specific diseases that affect the CNS by administering a compound that binds to microglial receptors and prevents or reduces microglial activation are described. ApoE receptor binding peptides that may be used in the methods of the invention are also described, as are methods of using such peptides to treat peripheral inflammatory conditions such as sepsis. Also described are methods of screening compds. for the ability to suppress or reduce microglial activation. Injection of ApoE (133-149) in mice suppressed serum levels of TNFα and IL-6 following LPS administration.

L16 ANSWER 31 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:854041 HCAPLUS
DOCUMENT NUMBER: 139:111447
TITLE: Therapeutic Drug Monitoring of Lamotrigine in Patients Suffering from Resistant Partial Seizures
AUTHOR(S): Benetello, Pierpaola; Furlanut, Marco; Baraldo, Massimo; Tonon, Agnese; Furlanut, Mario
CORPORATE SOURCE: Department of Neurological Sciences, University of Padua, Padua, Italy
SOURCE: European Neurology (2002), 48(4), 200-203
CODEN: EUNEAP; ISSN: 0014-3022
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sixty patients, all potential candidates for ongoing lamotrigine (LTG) treatment as add-on therapy for resistant partial seizures and receiving carbamazepine (CBZ) and/or valproate (VPA) treatment, were submitted to therapeutic drug monitoring (TDM). The aim was to evaluate the possible relation between serum levels and the clin. effect of LTG, to verify whether CNS toxicity has to be considered the result of a pharmacokinetic or a pharmacodynamic interaction with CBZ, and to





investigate whether possible changes in the clin. response during long-term treatment are dependent on LTG serum level variations. Sixteen patients achieved complete control, 25 a ≥50% reduction in seizures, the remainder did not respond. Mean LTG serum concns. were higher in responders than in nonresponders, the difference being statistically insignificant. The best results were observed in VPA-cotreated patients with the highest LTG blood levels. CNS toxicity occurred after giving LTG to subjects who subsequently developed the highest LTG concns., whereas CNS toxicity seemed unrelated to CBZ and CBZ-epoxide serum concns. No decrease in LTG, CBZ and VPA serum levels was observed even in patients showing a reduction in the response during long-term treatment.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 32 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:797249 HCAPLUS
DOCUMENT NUMBER: 139:299327
TITLE: Anticonvulsants in central pain
AUTHOR(S): Finnerup, Nanna B.; Gottrup, Hanne; Jensen, Troels S.
CORPORATE SOURCE: Department of Neurology and Danish Pain Research Centre, Aarhus University Hospital, Aarhus, 8000, Den.
SOURCE: Expert Opinion on Pharmacotherapy (2002), 3(10), 1411-1420
CODEN: EOPHP7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Treatment of central neuropathic pain (CP) following lesions of the CNS is a great challenge to the clinician. Preclin. and clin. studies indicate that neuronal hyperexcitability in damaged areas of the central nervous system plays a major role in the development of CP. Anticonvulsants are thought to act by increasing γ-aminobutyric acid-mediated inhibition, decreasing abnormal neuronal hyperexcitability by modulating sodium and calcium channels or by inhibiting excitatory amino acid actions. The resulting inhibition of excess neuronal activity is thought to be the basis for the use of anticonvulsants in epilepsy as well as neuropathic pain. Both first-generation anticonvulsant drugs (e.g., phenytoin, benzodiazepines, valproate and carbamazepine) and second-generation anticonvulsant drugs (e.g., lamotrigine, gabapentin and topiramate) are used in CP conditions. However, few randomized controlled trials on the treatment of this condition have been published. Present suggestions for anticonvulsant treatment of CP are lamotrigine as the first choice, followed by gabapentin or carbamazepine/oxcarbazepine. These compds. are considered as effective as the antidepressant amitriptyline.
REFERENCE COUNT: 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 33 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:672895 HCAPLUS
DOCUMENT NUMBER: 138:297430
TITLE: Lamotrigine derivatives and riluzole inhibit INa,P in cortical neurons
AUTHOR(S): Spadoni, Francesca; Hainsworth, Atticus Henry; Mercuri, Nicola Biagio; Caputi, Luigi; Martella, Giuseppina; Lavaroni, Franco; Bernardi, Giorgio; Stefani, Alessandro
CORPORATE SOURCE: IRCCS Fondazione Santa Lucia, Rome, Italy

SOURCE: NeuroReport (2002), 13(9), 1167-1170
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The persistent, slowly inactivating fraction of the sodium current (INa,P) is involved in key functions in the CNS such as dendritic integration of synaptic inputs and cellular excitability. We have studied whether established anti-epileptic drugs and neuroprotective agents target the persistent sodium current. Two lamotrigine deriva. (eipatrigine and 202W92) and riluzole inhibited the persistent sodium current at low, therapeutic concns. In contrast, lamotrigine and the classical antiepileptic agents phenytoin and valproic acid blocked the fast-inactivating sodium channel but failed to affect the persistent fraction. The ability to influence either mode of channel activity may represent a defining feature of each drug subclass, changing profoundly their clin. indications. Given the damaging role of a sustained influx of sodium in both pharmaco-resistant seizures or excitotoxic insults, we suggest the utilization of drugs that suppress the persistent conductance.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 34 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:488246 HCAPLUS
DOCUMENT NUMBER: 137:57576
TITLE: Methods and compositions using ion-dependent cotransporter modulators for treating conditions of the central and peripheral nervous systems using non-synaptic mechanisms
INVENTOR(S): Hochman, Daryl W.
PATENT ASSIGNEE(S): Cytoscan Sciences L.L.C., USA
SOURCE: U.S. Pat. Appl. Publ., 29 pp., Cont.-in-part of U.S. Ser. No. 470,637.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2002082252 | A1 | 20020627 | US 2002-56528 | | 20020123 |
| US 6495601 | B1 | 20021217 | US 1999-470637 | | 19991222 |
| US 2005267103 | A1 | 20051201 | US 2005-101000 | | 20050407 |
| US 2006025387 | A1 | 20060202 | US 2005-130945 | | 20050517 |
| US 2006089350 | A1 | 20060427 | US 2005-251724 | | 20051017 |
| US 2006035914 | A1 | 20060216 | US 2005-259532 | | 20051025 |
| PRIORITY APPLN. INFO.: | | | US 1998-113620P | P | 19981223 |
| | | | US 1999-470637 | A2 | 19991222 |
| | | | US 2001-263830P | P | 20010123 |
| | | | US 2002-56528 | A2 | 20020123 |
| | | | US 2005-101000 | A2 | 20050407 |
| | | | US 2005-130945 | A2 | 20050517 |

AB The invention discloses methods and compns. for treating selected conditions of the central and peripheral nervous systems employing non-synaptic mechanisms. More specifically, one aspect of the invention provides methods and materials for treating seizure and seizure disorders, epilepsy, status epilepticus, migraine, spreading depression, intracranial hypertension; for treating the pathophysiol. effects of head trauma,





stroke, ischemia and hypoxia; for treating or protecting from the pathophysiol. effects of neurotoxic agents such as ethanol; and for treating neurophsyciatric disorders and central nervous system edema by administering agents that modulate ionic concns. and/or ionic gradients in the brain, particularly ion-dependent or cation-chloride cotransporter antagonists. Electrolyte cotransport antagonists and combinations of such compns. with other agents for treating various conditions are disclosed. The invention also discloses methods and compns. for treating pain by administering ion-dependent cotransporter antagonists. Methods and compns. for enhancing cortical function, e.g. in centers of cognition, learning, and memory, by administering ion-dependent cotransporter agonists are disclosed.

L16 ANSWER 35 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:375796 HCAPLUS
DOCUMENT NUMBER: 137:5563
TITLE: Diet enriched with omega-3 fatty acids alleviates convulsion symptoms in epilepsy patients
AUTHOR(S): Schlanger, Simon; Shinitzky, Meir; Yam, Daniel
CORPORATE SOURCE: The Kalanit Institute for the Retarded Child, Rishon LeZion, Israel
SOURCE: Epilepsia (2002), 43(1), 103-104
CODEN: EPILAK; ISSN: 0013-9580
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We examined whether a dietary supplement containing omega-3 polyunsatd. fatty acids (n-3 PUFAs) can alleviate and/or reduce the frequency of epileptic seizures in patients with central nervous system (CNS) diseases treated with anticonvulsive drugs (ACDs). A special spread containing 65% n-3 PUFAs was added to the daily diet. The patients consumed 5 g of this spread at every breakfast for 6 mo. Five patients completed the study. In all of them, a marked reduction in both frequency and strength of the epileptic seizures was recorded. Incorporation of the dietary supplement containing n-3 PUFAs may be beneficial in suppression of some cases of epileptic seizures.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 36 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:195041 HCAPLUS
DOCUMENT NUMBER: 137:91443
TITLE: GABA and glutamate in migraine
AUTHOR(S): D'Andrea, Giovanni; Granella, Franco; Cataldini, Morena; Verdelli, Flavio; Balbi, Tiziana
CORPORATE SOURCE: Headache and Related Disorders Center, Pathology Unit, Este-Monselice Hospital, Este-Monselice, Italy
SOURCE: Journal of Headache and Pain (2001), 2(Suppl. 1), S57-S60
CODEN: JHPOAT; ISSN: 1129-2369
PUBLISHER: Springer-Verlag Italia Srl
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. GABA and glutamic acid are the main inhibitory and excitatory neurotransmitters of central nervous system. Among other functions they modulate the pain threshold in the CNS. For this reason it has been hypothesized that anomalies of GABA and glutamate turn-over may play a role in migraine pathogenesis. In this review are discussed the evidences in favor of this hypothesis. A derangement of GABA may be an





important factor in the occurrence of migraine attacks and their recurrence, whereas high level of glutamic acid may represent a biochem. marker of the neuronal hyperexcitability that may be the underlying cause of the aura. The pharmacol. modulation of metabolism of both neurotransmitters is a promising approach to improve migraine therapy. In particular the studies presented here suggest that gabaergic drugs may be useful in migraine without aura, antiglutamatergic drugs are indicated to treat migraine with aura.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 37 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:10280 HCAPLUS
DOCUMENT NUMBER: 136:64150
TITLE: GABA-ergic agonists for the treatment of age-related brain cortical dysfunction
INVENTOR(S): Leventhal, Audie G.
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002000221 | A1 | 20020103 | WO 2001-US19719 | 20010620 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2413405 | A1 | 20020103 | CA 2001-2413405 | 20010620 |
| AU 2001068609 | A5 | 20020108 | AU 2001-68609 | 20010620 |
| EP 1303280 | A1 | 20030423 | EP 2001-946582 | 20010620 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2004023952 | A1 | 20040205 | US 2002-311821 | 20021217 |
| AU 2006203432 | A1 | 20060831 | AU 2006-203432 | 20060809 |
| PRIORITY APPLN. INFO.: | | | US 2000-213388P | P 20000623 |
| | | | US 2001-277427P | P 20010320 |
| | | | WO 2001-US19719 | W 20010620 |

AB Methods are disclosed for the improvement of age-related decreases in cortical function by increasing the activity of inhibitory pathways, such as GABA-ergic pathways, in the central nervous system. In particular examples, subjects with age-related decreases in cortical function are treated by administration of therapeutically effective amts. of a GABA-ergic agonist. The disclosed methods also enable screening for drugs that inhibit an age-related decline in cortical function, for example by exposing a subject to a test agent, and measuring an increase in GABA-ergic cortical inhibitory activity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT





L16 ANSWER 38 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:904923 HCAPLUS
DOCUMENT NUMBER: 136:181219
TITLE: Effect of lamotrigine on the Ca2+-sensing cation current in cultured hippocampal neurons
AUTHOR(S): Xiong, Zhi-Gang; Chu, Xiang-Ping; MacDonald, J. F.
CORPORATE SOURCE: Robert S. Dow Neurobiology Laboratories, Legacy Clinical Research and Technology Center, Portland, OR, 97232, USA
SOURCE: Journal of Neurophysiology (2001), 86(5), 2520-2526
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

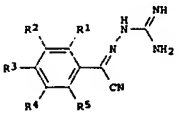
AB Concns. of extracellular calcium ([Ca2+]e) in the CNS decrease substantially during seizure activity. The authors have demonstrated previously that decreases in [Ca2+]e activate a novel calcium-sensing nonselective cation (csNSC) channel in hippocampal neurons. Activation of csNSC channels is responsible for a sustained membrane depolarization and increased neuronal excitability. This study has suggested that the csNSC channel is likely involved in generating and maintaining seizure activities. In the present study, the effects of anti-epileptic agent lamotrigine (LTG) on csNSC channels were studied in cultured mouse hippocampal neurons using patch-clamp techniques. At a holding potential of -60 mV, a slow inward current through csNSC channels was activated by a step reduction of [Ca2+]e from 1.5 to 0.2 mM. LTG decreased the amplitude of csNSC currents dose dependently with an IC50 of 171 ± 25.8 (SE) μM. The effect of LTG was independent of membrane potential. In the presence of 300 μM LTG, the amplitude of csNSC current was decreased by 31 ± 3% at -60 mV and 29 ± 2.9% at +40 mV ($P > 0.05$). LTG depressed csNSC current without affecting the potency of Ca2+ block of the current (IC50 for Ca2+ block of csNSC currents in the absence of LTG: 145 ± 18 μM; in the presence of 300 μM LTG: 136 ± 10 μM, $n = 5$, $P > 0.05$). In current-clamp recordings, activation of csNSC channel by reducing the [Ca2+]e caused a sustained membrane depolarization and an increase in the frequency of spontaneous firing of action potentials. LTG (300 μM) significantly inhibited csNSC channel-mediated membrane depolarization and the excitation of neurons. Fura-2 ratiometric Ca2+ imaging experiment showed that LTG also inhibited the increase in intracellular Ca2+ concentration induced by csNSC channel activation. The effect of LTG on csNSC channels may partially contribute to its broad spectrum of anti-epileptic actions.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 39 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:631908 HCAPLUS
DOCUMENT NUMBER: 135:195578
TITLE: Process for preparing substituted benzoyl cyanide amidinohydrazones as intermediates for synthesis of 3,5-diamino-6-phenyl-1,2,4-triazines
INVENTOR(S): Nadaka, Vladimir; Lexner, Jael; Kaspi, Joseph
PATENT ASSIGNEE(S): Chemagis Ltd., Israel
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1127873 | A2 | 20010829 | EP 2001-103660 | 20010223 |
| EP 1127873 | A3 | 20030507 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| IL 134730 | A | 20031031 | IL 2000-134730 | 20000225 |
| CA 2337280 | A1 | 20010825 | CA 2001-2337280 | 20010215 |
| HU 200100740 | A2 | 20011128 | HU 2001-740 | 20010215 |
| US 2001025118 | A1 | 20010927 | US 2001-789634 | 20010222 |
| US 6329521 | B2 | 20011211 | | |

PRIORITY APPLN. INFO.: IL 2000-134730 A 20000225
OTHER SOURCE(S): CASREACT 135:195578; MARPAT 135:195578
GI



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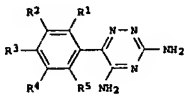
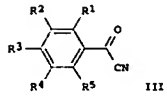


II



III

AB The title compds. [I; R1-R5 = H, halo, alkyl, etc.], useful as intermediates for synthesis of 1,2,4-triazines II (active in the treatment of CNS disorders), were prepared by reacting the benzoyl cyanides III with aminoguanidine bicarbonate in a mixture of a water-soluble solvent and polyphosphoric acid. Thus, reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in the presence of polyphosphoric acid in MeCN afforded 2,3-dichlorobenzoyl cyanide amidinohydrazone which was then heated under reflux in PrOH to give 2,3-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.



L16 ANSWER 40 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:237425 HCAPLUS
DOCUMENT NUMBER: 130:291518
TITLE: Analysis of CSF amino acids in young patients with generalized refractory epilepsy during an add-on study with lamotrigine
AUTHOR(S): Eriksson, Ann-Sofie; O'Connor, William T.
CORPORATE SOURCE: Department of Pediatrics, Karolinska Hospital, Stockholm, Sweden.
SOURCE: Epilepsy Research (1999), 34(1), 75-83
CODEN: EPIRES; ISSN: 0920-1211
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of add-on administration of lamotrigine (1-12 mg/kg per day, 2-12 mo) on the levels of neurotransmission related amino acids including γ-aminobutyric acid (GABA), glutamate, aspartate, glycine and antiepileptic drugs (AEDs) in lumbar cerebrospinal fluid (CSF) was studied in 22 children and young adults with generalized therapy resistant epilepsy. Two lumbar punctures were performed, one prior to, and one following a mean of 5 mo (2-12 mo) of lamotrigine treatment. Lamotrigine decreased seizure incidence and severity in 12 of the 22 patients without influencing CSF GABA, glutamate, aspartate or glycine levels. Lamotrigine did not alter the concns. of AEDs in CSF or plasma. However, CSF GABA levels were 86% higher in those patients also treated with γ-vinyl-GABA (vigabatrin, GVG) compared with patients treated with other combinations and this was not altered by co-medication with lamotrigine. The proposed mechanism of action of lamotrigine, namely that it may inhibit glutamate release in the CNS, is not reflected by changes in CSF glutamate levels. The present findings indicate that CSF GABA, glutamate, aspartate and glycine levels may not be useful as in vivo neurochem. markers in young patients responding to the therapeutic dose of lamotrigine used in this study.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L16 ANSWER 41 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:567031 HCAPLUS
DOCUMENT NUMBER: 129:270545
TITLE: Mechanisms of deafferentation-induced plasticity in human motor cortex
AUTHOR(S): Ziemann, Ulf; Hallett, Mark; Cohen, Leonardo G.
CORPORATE SOURCE: Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892-1428, USA
SOURCE: Journal of Neuroscience (1998), 18(17), 7000-7007
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Deafferentation induces rapid plastic changes in the cerebral cortex, probably via unmasking of pre-existent connections. Several mechanisms may contribute, such as changes in neuronal membrane excitability, removal of local inhibition, or various forms of short- or long-term synaptic plasticity. To understand further the mechanisms involved in cortical plasticity, we tested the effects of CNS-active drugs in a plasticity model, in which forearm ischemic nerve block (INB) was combined with low-frequency repetitive transcranial magnetic stimulation (rTMS) of the deafferented human motor cortex. RTMS was used to upregulate the plastic changes caused by INB. We studied six healthy subjects. In two control sessions without drug application, INB plus rTMS increased the motor-evoked potential (MEP) size and decreased intracortical inhibition (ICI) measured with single- and paired-pulse TMS in the biceps brachii muscle proximal to INB. A single oral dose of the benzodiazepine lorazepam (2 mg) or the voltage-gated $Na^+$ and $Ca^{2+}$ channel blocker lamotrigine (300 mg) abolished these changes. The NMDA receptor blocker dextromethorphan (150 mg) suppressed the reduction in ICI but not the increase





in MEP size. With sleep deprivation, used to eliminate sedation as a major factor of these drug effects, INB plus rTMS induced changes similar to that seen in the control sessions. The findings suggest that (1) the INB plus rTMS-induced increase in MEP size involves rapid removal of GABA-related cortical inhibition and short-term changes in synaptic efficacy dependent on $Na^+$ or $Ca^{2+}$ channels and that (2) the long-lasting (>60 min) reduction in ICI is related to long-term potentiation-like mechanisms given its duration and the involvement of NMDA receptor activation.
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 42 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:105002 HCAPLUS
DOCUMENT NUMBER: 128:213312
TITLE: Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction?
AUTHOR(S): Besag, F. M. C.; Berry, D. J.; Pool, F.; Newbery, J. E.; Subel, B.
CORPORATE SOURCE: St Piers Lingfield, Surrey, RH7 6PW, UK
SOURCE: Epilepsia (1998), 39(2), 183-187
CODEN: EPILAK; ISSN: 0013-9580
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to determine whether the toxicity that occurs in some patients when lamotrigine (LTG) is added to carbamazepine (CBZ) is the result of either a pharmacokinetic or a pharmacodynamic interaction, escalating LTG doses were added to ongoing CBZ treatment in 47 patients. All patients had blood samples collected for drug concentration measurement, including the epoxide metabolite of CBZ, before starting LTG treatment and after stabilizing at each dose escalation. Patients also were examined for signs of toxicity. After LTG was introduced, nine patients demonstrated clin. signs of CNS toxicity, mainly diplopia and dizziness. There was no significant ($p = 0.05$) change in the serum concns. of either CBZ or its epoxide metabolite when LTG was added either to the group as a whole or to the nine patients who experienced adverse CNS effects. LTG serum concns. also were below the level at which the common signs of LTG toxicity, such as nausea, vomiting, or unsteadiness, are more likely to occur. In seven of the nine patients who exhibited CNS toxicity, CBZ serum concns. were >8 mg/L on LTG introduction. Toxicity is more likely to occur when LTG is added to CBZ if the initial CBZ level is high, typically >8 mg/L. This appears to be the result of a pharmacodynamic interaction. A reduction of CBZ dose usually resolves the toxicity, allowing the LTG dose to be escalated to maximal effect. It is not usually necessary to stop either drug.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 43 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:638497 HCAPLUS
DOCUMENT NUMBER: 125:315860
TITLE: Lamotrigine monotherapy: An overview
AUTHOR(S): Brodie, M. J.
CORPORATE SOURCE: WESTERN INFIRMARY, UNIVERSITY DEPARTMENT MEDICINE AND THERAPEUTICS, Glasgow, UK
SOURCE: International Congress and Symposium Series - Royal Society of Medicine (1996), 214(Lamotrigine--A





Brighter Future), 43-49
CODEN: RMISDU; ISSN: 0142-2367
PUBLISHER: Royal Society of Medicine Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with .apprx.5 refs. In a pooled population of 784 patients with newly-diagnosed epilepsy participating in comparative monotherapy trials, 443 were randomized to lamotrigine, 246 to carbamazepine and 95 to phenytoin. Overall, fewer patients were withdrawn due to adverse events on lamotrigine than with the older drugs (lamotrigine 9.5%, carbamazepine 19.1%, phenytoin 18.9%). Central nervous system (CNS) problems resulting in withdrawal, in particular, were infrequent with lamotrigine (lamotrigine 2.5%, carbamazepine 7.7%, phenytoin 7.4%). Withdrawal due to rash occurred in 6.1% of patients on lamotrigine, 8.9% on carbamazepine and 5.3% on phenytoin. The rash rate leading to withdrawal with lamotrigine appeared to relate to the initiation dose (100 mg, 11.8%; 50 mg, 9.2%; 25 mg, 2.2%). It is sometimes appropriate to substitute lamotrigine monotherapy for other antiepileptic drug treatments. Schedules for substituting lamotrigine in patients established on phenytoin, carbamazepine or sodium valproate are outlined. In the comparative monotherapy trials, the most popular lamotrigine doses were 150-200 mg daily. In studies in which concomitant antiepileptic drugs (AEDs) were withdrawn to achieve lamotrigine monotherapy, some patients took as much as 700 mg lamotrigine daily. Clin. experience to date does not suggest the existence of a relationship between the plasma lamotrigine concentration and its efficacy or toxicity. Data and case reports from a prospective study in Glasgow relating lamotrigine dosage and concentration to seizure control and the emergence of side effects are presented.

L16 ANSWER 44 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:94551 HCAPLUS
DOCUMENT NUMBER: 124:194132
TITLE: The effects of anticonvulsants on 4-aminopyridine-induced bursting: in vitro studies on rat peripheral nerve and dorsal roots
AUTHOR(S): Lees, G.
CORPORATE SOURCE: Dep. Academic Anaesthetics, Imperial College Medicine, London, W2 1NY, UK
SOURCE: British Journal of Pharmacology (1996), 117(3), 573-9
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aminopyridines have been used as beneficial symptomatic treatments in a variety of neurol. conditions including multiple sclerosis but have been associated with considerable toxicity in the form of abdominal pain, paraesthesias and (rarely) convulsions. Extracellular and intracellular recording was used to characterize action potentials in rat sciatic nerves and dorsal roots and the effects of 4-aminopyridine (4-AP). In sciatic nerve trunks, 1 mM 4-AP produced pronounced after potentials at room temperature secondary to regenerative firing in affected axons (5-10 spikes per stimulus). At physiol. temps., after potentials (2-3 spikes) were greatly attenuated in peripheral axons. 4-AP evoked more pronounced and prolonged after discharges in isolated dorsal roots at 37°C (3-5.5 mV and 80-100 ms succeeded by a smaller inhibitory/depolarizing voltage shift) which were used to assess the effects of anticonvulsants. Phenytoin, carbamazepine and lamotrigine dose-dependently reduced the area of 4-AP-induced after potentials at 100 and 320 μM but the amplitude of

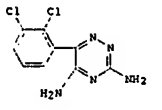
compound action potentials (evoked at 0.5 Hz) was depressed in parallel. The tonic block of sensory action potentials by all three drugs (at 320 μM) was enhanced by high frequency stimulation (5-500 Hz). The lack of selectivity of these frequency-dependent Na+ channel blockers for burst firing, compared to low-frequency spikes, is discussed in contrast to their effects on 4-AP-induced seizures and paroxysmal activity in CNS tissue (which is associated with large and sustained depolarizing plateau potentials). In conclusion, these in vitro results confirm the marked sensitivity of sensory axons to 4-AP (the presumptive basis for paraesthesias). Burst firing was not preferentially impaired at relatively high concns. suggesting that anticonvulsants will not overcome the toxic peripheral actions of 4-AP in neurol. patients.

L16 ANSWER 45 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:531450 HCAPLUS
DOCUMENT NUMBER: 119:131450
TITLE: Studies on the mechanism of action of the novel anticonvulsant lamotrigine (Lamictal) using primary neuroglial cultures from rat cortex
AUTHOR(S): Lees, George; Leach, Michael J.
CORPORATE SOURCE: Dep. Pharmacol., Wellcome Res. Lab., Beckenham/Kent, BR3 3BS, UK
SOURCE: Brain Research (1993), 612(1-2), 190-9
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Whole cell and perforated patch clamp expts. were conducted on cultured cortical rat neurons (7-21 days in vitro) in order to determine the effects of the anticonvulsant and glutamate release inhibitor lamotrigine (10-100 μM), on CNS receptors and ion channels. The compound inhibited, indiscriminately, both excitatory and inhibitory synaptic events which occurred spontaneously in cultured neural circuits. The drug did not mimic diazepam as a pos. modulator of GABAA currents. In the presence of tetrodotoxin, voltage-gated potassium currents and composite currents evoked by L-glutamate were not significantly modulated even at the highest dose. Unitary, fast, presumptive-sodium spikes, evoked at low frequencies, were not blocked significantly by lamotrigine. In contrast, burst firing induced by pulsed application of L-glutamate or potassium ions was markedly depressed at 10 μM. Presumptive calcium currents were inhibited by lamotrigine at 100 μM. It is proposed that the drug inhibits epileptiform burst firing preferentially by state/activity dependent interactions with voltage and gated cation channels. Potential mechanisms for inhibition of glutamate release are discussed.

L16 ANSWER 46 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:102360 HCAPLUS
DOCUMENT NUMBER: 104:102360
TITLE: Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam
AUTHOR(S): Cohen, A. F.; Ashby, L.; Crowley, D.; Land, G.; Peck, A. W.; Miller, A. A.
CORPORATE SOURCE: Wellcome Res. Lab., Beckenham/Kent, UK
SOURCE: British Journal of Clinical Pharmacology (1985), 20(6), 619-29
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English
GI







I

AB Healthy male volunteers received phenytoin [57-41-0] 0.5 and 1 g, lamotrigine (I) [84057-84-1] (a new anticonvulsant) 120 and 240 mg, diazepam [439-14-5] 10 mg and placebo orally in a double-blind, cross-over, randomized trail. Maximum drug concns. at 4 h, measured in plasma were 11.5 μg/mL for phenytoin and 2.7 μg/mL for lamotrigine. These levels were in the therapeutic range for phenytoin and the putative therapeutic range for lamotrigine. Side effects after diazepam (mainly sedation) and phenytoin (mainly unsteadiness) differed markedly from lamotrigine which produced no important side effects. Subjective effects as measured by visual analog scales were caused by phenytoin and diazepam but not by lamotrigine. Diazepam impaired eye movements, adaptive tracking and body sway. Phenytoin impaired adaptive tracking, increased body sway and impaired smooth pursuit eye movement. Lamotrigine produced only a possible slight increase in body sway. There were significant correlations between performance and saliva levels of phenytoin and diazepam. The tests used were suitable for monitoring central nervous system (CNS) effects of anticonvulsants and lamotrigine possibly could have a more favorable CNS side effect than phenytoin.

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L1 STRUCTURE UPLOADED
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L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
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L5 0 S E3/RN
L6 1 S E3

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7 0 S L6

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
E LAMOTRIGINE+ALL/CT
S LAMOTRIGINE/CN

FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8 1 S LAMOTRIGINE/CN

FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9 1265 S L8





L10 27 S "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
L11 1 S 84057-84-1/RN

FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007
L12 1265 S L11
L13 111187 S L10 OR L12 AND PARTICLE OR GRANULE
L14 0 S L12 (N) PARTICLE
L15 0 S L12 (W) PARTICLE
L16 46 S L12 AND CNS

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=> s aronhime,j?/au or samburski,g?/au
           86 ARONHIME,J?/AU
            8 SAMBURSKI,G?/AU
L17        91 ARONHIME,J?/AU OR SAMBURSKI,G?/AU

=> s aronhime,j?/au and samburski,g?/au
           86 ARONHIME,J?/AU
            8 SAMBURSKI,G?/AU
L18         3 ARONHIME,J?/AU AND SAMBURSKI,G?/AU

=> d l18 1-3 ibib abs

L18  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2007:259910  HCAPLUS
DOCUMENT NUMBER:         146:281059
TITLE:                   Solid particulate tadalafil having a bimodal particle
                         size distribution
INVENTOR(S):             Aronhime, Judith; Samburski, Guy;
                         Ovadya, Yhoshoa
PATENT ASSIGNEE(S):      Teva Pharmaceutical Industries Ltd., Israel; Teva
                         Pharmaceuticals USA, Inc.
SOURCE:                  PCT Int. Appl., 19pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2007027612         A2    20070308    WO 2006-US33541         20060829
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
             KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
             MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
             RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                       US 2005-712589P     P  20050829
AB   Provided is a solid particulate tadalafil having a bimodal particle size
     distribution.  The solid particulate tadalafil is useful for the manufacture of
     a medicament for the treatment of sexual dysfunction.  Thus, 2 g of a
     solid particulate tadalafil having a bimodal particle size distribution
     were prepared by combining 0.38 g of large particle size tadalafil and 1.62
     g of small particle size tadalafil.  Calcn. of the amount of large particle
     size particulate tadalafil was presented.

L18  ANSWER 2 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2006:543943  HCAPLUS
DOCUMENT NUMBER:         145:45919
TITLE:                   Process for the preparation of ezetimibe polymorphic
                         crystalline forms
INVENTOR(S):             Aronhime, Judith; Koltai, Tamas;
                         Samburski, Guy; Lehrman, Ori; Izsak, Reuven
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PATENT ASSIGNEE(S):      Teva Pharmaceutical Industries Ltd., Israel; Teva
                         Pharmaceuticals Usa, Inc.
SOURCE:                  PCT Int. Appl., 54 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2006060808         A1    20060608    WO 2005-US44065         20051205
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX,
             MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
             SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
             VN, YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
     US 2006160785         A1    20060720    US 2005-295141          20051205
PRIORITY APPLN. INFO.:                       US 2004-632543P     P  20041203
                                             US 2005-649139P     P  20050203
                                             US 2005-668571P     P  20050406
                                             US 2005-687316P     P  20050606
                                             US 2005-712781P     P  20050830
                                             US 2005-717275P     P  20050914
AB   Processes are described for preparing polymorphic crystalline forms of
ezetimibe,
     such as ezetimibe Form A or Form B, for example, by precipitating ezetimibe
from
     selected solvents.  Some forms may be transformed into different forms at
     elevated temps., or under various humidity conditions, or by
     micronization.
REFERENCE COUNT:         8     THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18  ANSWER 3 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2003:875073  HCAPLUS
DOCUMENT NUMBER:         139:354488
TITLE:                   Pharmaceutical composition containing lamotrigine
                         particles of defined morphology
INVENTOR(S):             Aronhime, Judith; Samburski, Guy
PATENT ASSIGNEE(S):      Teva Pharmaceutical Industries Ltd., Israel; Teva
                         Pharmaceuticals USA, Inc.
SOURCE:                  PCT Int. Appl., 24 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    -------------------     --------
     WO 2003090693         A2    20031106    WO 2003-US13002         20030423
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# EAST Search History

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
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| S1 | 0 | lamotrigene same particle adj size | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 07:32 |
| S2 | 7 | lamotrigene | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:24 |
| S3 | 23310 | particles same specific adj surface adj area | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:04 |
| S4 | 163 | S3 and pharmaceutical adj composition | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:51 |
| S5 | 0 | lamotrigene same Teva adj Pharmaceutical? | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:54 |
| S6 | 0 | lamotrigene same Teva | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/23 17:52 |
| S7 | 1 | ("3090693").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/23 18:21 |
| S8 | 1 | ("5861179").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/23 18:21 |
| S9 | 0 | bet near particle adj size near surface adj area | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 07:33 |
| S10 | 1134 | particle adj size near surface adj area | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 07:43 |
| S11 | 3 | S10 and BET adj measure? | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2006/08/24 12:25 |
| S12 | 3 | (("4847249") or ("5942510") or ("5861179")).PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 12:31 |
| S13 | 1 | ("4602017").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 15:06 |

# EAST Search History

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| S14 | 1 | ("0021121").PN. | US-PGPUB; USPAT | OR | OFF | 2006/08/24 15:08 |
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| S18 | 3731 | S17 and @ad<="20030801" | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:07 |
| S19 | 160 | ((JUDITH) near2 (ARONHIME)).INV. | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:49 |
| S20 | 5 | ((GUY) near2 (SAMBURSKI)).INV. | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 15:20 |
| S21 | 88 | ((JUDITH) near2 (ARONHIME)).INV. | EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:21 |
| S22 | 6 | ((GUY) near2 (SAMBURSKI)).INV. | EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:21 |
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| S26 | 8 | "LAMOTRIGENE" | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:29 |
| S27 | 0 | "6-(2,3-dichlorophenyl)-1,2, 4-triazine-3,5-diamine" | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2007/04/04 15:44 |
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| S36 | 91 | S34 and @ad<="20030801" | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:08 |
| S37 | 0 | ("5861179").URPN. | USPAT | OR | ON | 2007/04/04 16:09 |
| S38 | 1 | ("5912345").URPN. | USPAT | OR | ON | 2007/04/04 16:10 |
| S39 | 38 | S36 and particl?? | US-PGPUB; USPAT; USOCR | OR | ON | 2007/04/04 16:15 |

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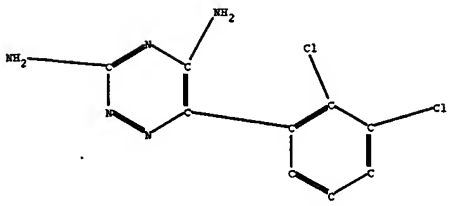
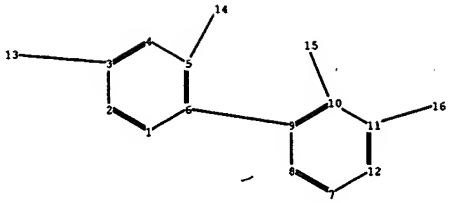
STN
lwl
4/4/07





chain nodes :
13 14 15 16
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
3-13 5-14 6-9 10-15 11-16
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
3-13 5-14
exact bonds :
6-9 10-15 11-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS

10/511987 LAMOTRIGINE reg no-text search USPGPUB search

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=> d his

     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

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L1                STRUCTURE UPLOADED
L2              3 S L1 SSS SAM
L3            128 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4             25 S L3/P
                  E US20050238724/PN,PRN,AN
L5              0 S E3/RN
L6              1 S E3

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L7              0 S L6

     FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
                  E LAMOTRIGINE+ALL/CT
                  S LAMOTRIGINE/CN

     FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8              1 S LAMOTRIGINE/CN

     FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9           1265 S L8
L10            27 S "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

     FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
L11             1 S 84057-84-1/RN

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L13        111187 S L10 OR L12  AND PARTICLE OR GRANULE
L14             0 S L12 (N) PARTICLE
L15             0 S L12 (W) PARTICLE
L16            46 S L12 AND CNS
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10/511987 LAMOTRIGINE reg no-text search USPGPUB search

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L1 STRUCTURE UPLOADED

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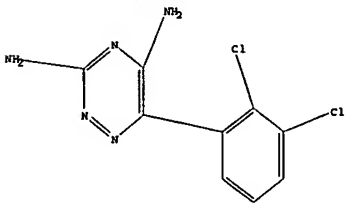
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 9 TO 360
PROJECTED ANSWERS: 3 TO 163

L2 3 SEA SSS SAM L1

=> d l2 1-3 ibib abs
'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
FIDE - All substance data, except sequence data
IDE - FIDE, but only 50 names
SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD - Protein sequence data, includes RN



10/511987 LAMOTRIGINE reg no-text search USPGPUB search

SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

CALC - Table of calculated properties
EPROP - Table of experimental properties
PROP - EPROP and CALC

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

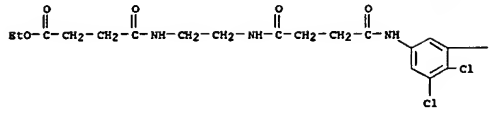
HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):ide

L2 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 865316-75-6 REGISTRY
ED Entered STN: 23 May 2006
CN Butanoic acid, 4-[[2-[[4-[[3,4-dichloro-5-(3,5-diamino-1,2,4-triazin-6-yl)phenyl]amino]-1,4-dioxobutyl]amino]ethyl]amino]-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)
MF C21 H26 Cl2 N8 O5
SR CA
LC STN Files: CA, CAPLUS



10/511987 LAMOTRIGINE reg no-text search USPGPUB search

PAGE 1-A



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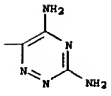

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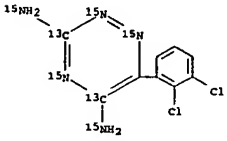
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 478189-71-8 REGISTRY
ED Entered STN: 06 Jan 2003
CN 1,2,4-Triazine-3,5-diamine-3,5-13C2-N,N',1,2,4-15N5, 6-(2,3-dichlorophenyl)- (9CI) (CA INDEX NAME)
MF C9 H7 Cl2 N5
SR CA
LC STN Files: CA, CAPLUS, CASREACT



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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 454695-04-6 REGISTRY
ED Entered STN: 25 Sep 2002
CN Formamide, N,N-dimethyl-, compd. with 6-(2,3-dichlorophenyl)-1,2,4-



10/511987 LAMOTRIGINE reg no-text search USPGPUB search

triazine-3,5-diamine (3:2) (9CI) (CA INDEX NAME)
MF C9 H7 Cl2 N5 . 3/2 C3 H7 N O
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

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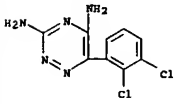
CRN 84057-84-1
CMF C9 H7 Cl2 N5



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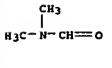
CMF C3 H7 N O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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SEARCH TIME: 00.00.01

L3 128 SEA SSS FUL L1

=> fil hcaplus
COST IN U.S. DOLLARS SINCE FILE ENTRY 178.40 TOTAL SESSION 178.61

FULL ESTIMATED COST

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 4 Apr 2007 VOL 146 ISS 15
FILE LAST UPDATED: 3 Apr 2007 (20070403/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his

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L2 3 S L1 SSS SAM
L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007

=> s l3/p
L4 25 L3/P

=> d l4 1-25 ibib abs

L4 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:411970 HCAPLUS
DOCUMENT NUMBER: 144:425648
TITLE: Lamotrigine analogs for production of anti-lamotrigine antibodies and use as immunoassay reagents
INVENTOR(S): Ouyang, Anlong; Arabshahi, Lili; Roberts, Mark; Wall, Melissa
PATENT ASSIGNEE(S): Seradyn, Inc., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006047372 | A2 | 20060504 | WO 2005-US38100 | 20051021 |
| WO 2006047372 | A3 | 20060727 | | |
| WO 2006047372 | A9 | 20061005 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW





RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2006115865 A1 20060601 US 2005-254650 20051020
PRIORITY APPLN. INFO.: US 2004-621764P P 20041025
US 2005-254650 A 20051020

OTHER SOURCE(S): MARPAT 144:425648
AB The invention discloses lamotrigine analogs that have substituents at the triazine 3-position and on the benzene 4-position and 5-position. The lamotrigine analogs can include immunogenic moieties that can be used to prepare anti-lamotrigine antibodies, or antigenic moieties that can be used in immunodiagnostic assays for lamotrigine. Also, the lamotrigine analog can include tracer moieties for detecting the presence or amount of the analog during an immunodiagnostic assay. Addnl., the lamotrigine analogs can be used in immunodiagnostic assays to compete with lamotrigine for binding with anti-lamotrigine antibodies. Lamotrigine analog preparation is described.

L4 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:411913 HCAPLUS
DOCUMENT NUMBER: 144:425647
TITLE: Immunoassays for lamotrigine
INVENTOR(S): Ouyang, Anlong; Arabshahi, Lili; Roberts, Mark; Wall, Melissa
PATENT ASSIGNEE(S): Seradyn, Inc., USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006047451 | A2 | 20060504 | WO 2005-US38258 | 20051021 |

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2006172356 A1 20060803 US 2005-254637 20051020
PRIORITY APPLN. INFO.: US 2004-621764P P 20041025
US 2005-254637 A 20051020

OTHER SOURCE(S): MARPAT 144:425647
AB Generally, the present invention relates to lamotrigine analogs that have substituents at the triazine 3-position and on the benzene 4-position and 5-position. The lamotrigine analogs can include immunogenic moieties that can be used to prepare anti-lamotrigine antibodies, or antigenic moieties that can be used in immunodiagnostic assays for lamotrigine. Also, the lamotrigine analog can include tracer moieties for detecting the presence





or amount of the analog during an immunodiagnostic assay. Addnl., the lamotrigine analogs can be used in immunodiagnostic assays to compete with lamotrigine for binding with anti-lamotrigine antibodies.

L4 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1010006 HCAPLUS
DOCUMENT NUMBER: 144:312050
TITLE: A new approach to the synthesis of lamotrigine and other 3,5-diamino-1,2,4-triazine derivatives
AUTHOR(S): Ulomskii, E. N.; Shestakova, T. S.; Deev, S. L.; Rusinov, V. L.; Chupakhin, O. N.
CORPORATE SOURCE: Ural State Technical University, Yekaterinburg, 620002, Russia
SOURCE: Russian Chemical Bulletin (2005), 54(3), 726-732
CODEN: RCBUEY; ISSN: 1066-5285
PUBLISHER: Springer Science+Business Media, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new in principle method for the synthesis of 6-aryl(hetaryl)-3,5-diamino-1,2,4-triazines by decomposition of pre-synthesized tetrazolo[1,5-b][1,2,4]triazines was developed. The advantages of this method over traditional methods were demonstrated using the synthesis of a modern antiepileptic preparation lamotrigine, as an example. The crystal structure of 6-phenyltetrazolo[1,5-b][1,2,4]triazin-7-amine is presented (monoclinic, space group P21/c, a 10.935(2), b 6.7330(10), c 13.279(3) Å, β 93.20(3)°, V 976.1(3) Å3, Z 4).
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:421792 HCAPLUS
DOCUMENT NUMBER: 142:430313
TITLE: Process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (Lamotrigine) via reaction of 2,3-dichlorobenzoyl chloride with cuprous cyanide and then with aminoguanidine bicarbonate followed by cyclization.
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): Torrent Pharmaceuticals Ltd., India
SOURCE: Indian, 12 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,





CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

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|---|---|---|---|---|
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |
| US 6111101 | A | 20000829 | US 1999-456501 | 19991208 |

PRIORITY APPLN. INFO.: IN 1998-CA2171 A 19981214
WO 1999-IB1955 W 19991207

OTHER SOURCE(S): CASREACT 142:430313
AB Lamotrigine was prepared by reaction of 2,3-dichlorobenzoyl chloride with CuCN (1:1-2 molar ratio) in MeCN and a cosolvent to produce dichlorobenzoyl cyanide, reaction of the latter with aminoguanidine bicarbonate to produce the cyanoimine intermediate 2-[cyano(2,3-dichlorophenyl)methylene]hydrazinecarboximidamide, and cyclization of this in the presence of aqueous KOH at 80°-reflux.

L4 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:421470 HCAPLUS
DOCUMENT NUMBER: 141:7119
TITLE: Preparation of crystalline lamotrigine and its monohydrate
INVENTOR(S): Manjunatha, Sulur G.; Kulkarni, Ashok Krishna; Kishore, Charugundla; Bokka, Ravisankar
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: Brit. UK Pat. Appl., 25 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| GB 2395483 | A | 20040526 | GB 2003-15608 | 20030703 |
| WO 2005003104 | A2 | 20050113 | WO 2004-IN186 | 20040628 |
| WO 2005003104 | A3 | 20050922 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-15608 A 20030703
OTHER SOURCE(S): CASREACT 141:7119
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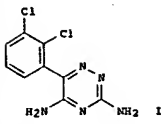

I

AB The invention relates to crystalline lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) (I) monohydrate and anhydrous lamotrigine. An improved process for manufacturing these products comprises reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in aqueous mineral acid, optionally together with a water miscible organic solvent, at 30-80° to produce the 2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (Schiff base) (II). The Schiff base II is further cyclized in aqueous organic solvent, e.g. alc. to produce pure lamotrigine of a pharmaceutically acceptable quality which on further drying at 45-50° under vacuum yields lamotrigine monohydrate, and/or on further drying at 100-110° yields anhydrous lamotrigine. The lamotrigine monohydrate or anhydrous lamotrigine thereby produced may then be brought into association with a pharmaceutically acceptable carrier for administration to a patient in need thereof.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:390214 HCAPLUS
DOCUMENT NUMBER: 140:391299
TITLE: Process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Dalmases Barjoan, Pere; Bessa Bellmunt, Jordi
PATENT ASSIGNEE(S): Laboratorios Vita, S.A., Spain
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004039767 | A1 | 20040513 | WO 2003-IB4763 | 20031027 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| ES 2209639 | A1 | 20040616 | ES 2002-2502 | 20021031 |





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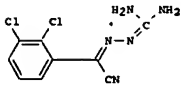
|---|---|---|---|---|
| ES 2209639 | B1 | 20050801 | | |
| AU 2003272019 | A1 | 20040525 | AU 2003-272019 | 20031027 |
| EP 1556341 | A1 | 20050727 | EP 2003-753860 | 20031027 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2006052625 | A1 | 20060309 | US 2005-532397 | 20050422 |
| US 7179913 | B2 | 20070220 | | |
| NO 2005002574 | A | 20050527 | NO 2005-2574 | 20050527 |
| PRIORITY APPLN. INFO.: | | | ES 2002-2502 | A 20021031 |
| | | | WO 2003-IB4763 | W 20031027 |

OTHER SOURCE(S): CASREACT 140:391299
GI



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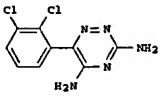


II

AB A method for preparing the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile (I; m.p. 180-183°) which comprises the condensation reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a non-aqueous medium in the presence of methanesulfonic acid, which produces good I yields and short reaction times. I is cyclized into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (II; m.p. 217°) under reflux in an aliph alc. (e.g., ethanol) or alc.-water mixture
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:267313 HCAPLUS
DOCUMENT NUMBER: 140:303705
TITLE: Two-step process for the synthesis of high-purity 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine from 2,3-dichlorobenzoyl cyanide and aminoguanidine dimesylate





INVENTOR(S): Neu, Jozsef; Gizur, Tibor; Toerley, Jozsef; Csabai, Janos; Vegh, Ferenc; Kalvin, Peter; Tarkanyi, Gabor
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004026845 | A1 | 20040401 | WO 2003-HU72 | 20030918 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| HU 200203114 | A2 | 20040528 | HU 2002-3114 | 20020920 |
| CA 2498761 | A1 | 20040401 | CA 2003-2498761 | 20030918 |
| AU 2003267676 | A1 | 20040408 | AU 2003-267676 | 20030918 |
| EP 1539720 | A1 | 20050615 | EP 2003-748368 | 20030918 |
| EP 1539720 | B1 | 20061122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| AT 346051 | T | 20061215 | AT 2003-748368 | 20030918 |
| IN 2005KN00267 | A | 20060714 | IN 2005-KN267 | 20050224 |
| US 2006178511 | A1 | 20060810 | US 2005-528379 | 20051129 |
| PRIORITY APPLN. INFO.: | | | HU 2002-3114 | A 20020920 |
| | | | WO 2003-HU72 | W 20030918 |

OTHER SOURCE(S): CASREACT 140:303705
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB High-purity 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I; i.e., lamotrigine) is prepared by the condensation reaction of 2,3-dichlorobenzoyl cyanide (II) with 1-2 mol equivalent of an aminoguanidine salt (e.g., aminoguanidine dimesylate) in 3-6 mol equivalent of methanesulfonic acid, then the obtained adduct (III) is transformed without isolation into the desired product by contacting it with magnesium oxide, followed by crystallization of the product from an appropriate organic solvent (e.g., acetone).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:507707 HCAPLUS
DOCUMENT NUMBER: 139:69292
TITLE: Process for the preparation of lamotrigine and related 3,5-diamino-6-substituted-1,2,4-triazines via

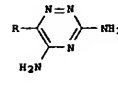




cyclization of cyanoiminoguanidines.
INVENTOR(S): Guntoori, Bhaskar Reddy; Che, Daqing; Murthy, K. S. Keshava
PATENT ASSIGNEE(S): Brantford Chemicals Inc., Can.
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6586593 | B1 | 20030701 | US 2002-46383 | 20020116 |
| CA 2366521 | A1 | 20030624 | CA 2001-2366521 | 20011224 |
| CA 2366521 | C | 20070306 | | |
| WO 2003078407 | A1 | 20030925 | WO 2002-CA1926 | 20021218 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002367765 | A1 | 20030929 | AU 2002-367765 | 20021218 |
| EP 1458692 | A1 | 20040922 | EP 2002-807048 | 20021218 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| NZ 533734 | A | 20051223 | NZ 2002-533734 | 20021218 |
| PRIORITY APPLN. INFO.: | | | CA 2001-2366521 | A 20011224 |
| | | | WO 2002-CA1926 | W 20021218 |

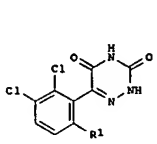
OTHER SOURCE(S): CASREACT 139:69292; MARPAT 139:69292
GI



I

AB Title compds. [I; R = (substituted) alkyl, aryl], were prepared by reaction of RCOCN with aminoguanidine in the presence of an organic sulfonic acid in an organic solvent under anhydrous conditions to give (HO)C(R)(CN)NHNC(NH2)2, dehydration of this to give NCC(R){:NN:C(NH2)2}, and cyclization of the latter. Thus, aminoguanidine hydrochloride in DMF was treated with MeSO3H and 2,3-dichlorobenzoyl chloride followed by stirring for 1 h, addition of SOCl2, and stirring for 1 h to give 39.2% iminoguanidine derivative The latter was refluxed with KOH in Me2CHOH to give 82% lamotrigine monohydrate.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:385795 HCAPLUS
DOCUMENT NUMBER: 140:199296
TITLE: Synthesis of oxo analogs of Lamotrigine and related compounds
AUTHOR(S): Hlavac, Jan; Buchtik, Roman; Slouka, Jan; Hradil, Pavel; Wiedermannova, Iveta
CORPORATE SOURCE: Department of Organic Chemistry, Palacky University, Olomouc, CZ-771 46, Czech Rep.
SOURCE: ARKIVOC (Gainesville, FL, United States) (2003), (1), 22-28
CODEN: AGFUAR
URL: http://www.arkat-usa.org/ark/journal/2003/General/2-556F/556F.pdf
PUBLISHER: Arkat USA Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:199296
GI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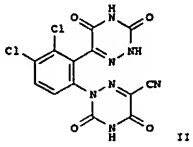
II

AB Lamotrigine oxo analogs I (R1 = H, Cl, Br, iodo, HO) were prepared from azauracil I (R1 = NH2) via the formation of the intermediate diazonium salt. Coupling of this diazonium salt with Et cyanoacetylcarbamate gave the corresponding carbamoyl hydrazone, which underwent intramol. cyclization upon reflux in pyridine to afford bis(triazinyl)benzene II containing two 6-azauracil rings.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:334629 HCAPLUS
DOCUMENT NUMBER: 138:343869
TITLE: Novel pharmaceutical compounds containing drugs bound to polypeptides
INVENTOR(S): Picariello, Thomas
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 4662 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 24
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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|---|---|---|---|---|
| WO 2003034980 | A2 | 20030501 | WO 2001-US43089 | 20011114 |
| WO 2003034980 | A8 | 20051103 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2428971 | A1 | 20030501 | CA 2001-2428971 | 20011114 |
| EP 1401374 | A1 | 20040331 | EP 2001-274606 | 20011114 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2006516948 | T | 20060713 | JP 2003-537549 | 20011114 |
| US 2004063628 | A1 | 20040401 | US 2002-156527 | 20020529 |
| US 7060708 | B2 | 20060613 | | |
| US 2007060500 | A1 | 20070315 | US 2006-392678 | 20060330 |
| PRIORITY APPLN. INFO.: | | | US 2000-274622P | P 20001114 |
| | | | US 1999-265415 | B2 19990310 |
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| | | | US 2001-987458 | B2 20011114 |
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| | | | US 2002-156527 | A2 20020529 |
| | | | US 2003-507012P | P 20030930 |
| | | | US 2004-567800P | P 20040505 |
| | | | US 2004-567802P | P 20040505 |
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| | | | US 2004-923088 | A2 20040823 |
| | | | WO 2004-US32131 | A2 20040930 |

AB Compns. comprising polypeptides and drugs covalently attached to the polypeptide are disclosed. Also provided is a method for delivery of these drugs to a patient comprising administering to the patient a composition comprising a polypeptide and a drug covalently attached to the polypeptide. Also provided is a method for protecting drugs from degradation comprising covalently attaching them to a polypeptide. Also provided is a method for controlling release of drugs from a composition comprising covalently attaching them to the polypeptide.

L4 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:76761 HCAPLUS
DOCUMENT NUMBER: 138:137336
TITLE: Method for producing lamotrigine from alpha-oxo-2,3-dichlorophenylacetamidinoaminoguanidino hydrazone by ring closure reaction
INVENTOR(S): Schneider, Geza; Gegoe, Csaba Lehel; Ondi, Levente; Mate, Attila Gergely; Lukacs, Ferenc; Nyerges, Miklos; Garaczi, Sandor
PATENT ASSIGNEE(S): Helm AG, Germany; CF Pharma Gyogyszergyarto Kft.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

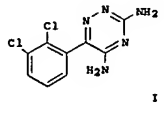
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003006393 | A1 | 20030130 | WO 2002-EP7433 | 20020704 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10134980 | A1 | 20030213 | DE 2001-10134980 | 20010717 |
| DE 10134980 | C2 | 20030528 | | |
| EP 1311492 | A1 | 20030521 | EP 2002-758308 | 20020704 |
| EP 1311492 | B1 | 20040908 | | |





| | | | | |
|---|---|---|---|---|
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE | | | | |
| CA 2417435 | C | 20040113 | CA 2002-2417435 | 20020704 |
| CA 2417435 | A1 | 20030130 | | |
| ES 2224074 | T3 | 20050301 | ES 2002-2756308 | 20020704 |
| US 2003191310 | A1 | 20031009 | US 2003-343225 | 20030515 |
| US 6683182 | B2 | 20040127 | | |
| PRIORITY APPLN. INFO.: | | | DE 2001-10134980 | A 20010717 |
| | | | WO 2002-EP7433 | W 20020704 |

OTHER SOURCE(S): CASREACT 138:137336; MARPAT 138:137336
GI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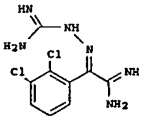
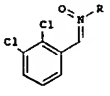
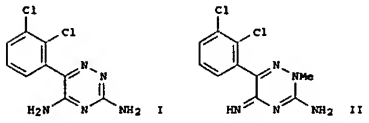

II


III

AB The invention relates to a method for producing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine [lamotrigine (I)], or its pharmaceutically acceptable salts, by ring closure reaction from α-oxo-2,3-dichlorophenylacetamidinoaminoguanidino hydrazone (II) or its salts. The preparation of II from N-oxides, III [R = linear, branched or cyclic (un)substituted alkyl, aryl, aralkyl], or their salts, are also described. Thus, I was prepared from 2,3-Cl2C6H3CH:N(O)Ph, via cyanation with NaCN, amination to the acetamidine hydrochloride, reaction with aminoguanine bicarbonate to give II·HCl, treatment with aqueous NaOH to give the free base, which is cyclized to I; cyclization of II·HCl gives I·HCl.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:549362 HCAPLUS
DOCUMENT NUMBER: 138:24695
TITLE: Synthesis of stable isotopically labelled versions of Lamotrigine and its methylated metabolite
AUTHOR(S): Manning, Calvin O.; Wadsworth, Alan H.; Fellows, Ian

CORPORATE SOURCE: Chemical Development, GlaxoSmithKline Research and Development, Stevenage, SG1 2NY, UK
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (2002), 45(7), 611-618
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:24695
GI



AB Lamotrigine (I) is a sodium channel antagonist used for the treatment of epilepsy. Stable isotopically labeled [M + 7] analogs of I and of its N-methylated metabolite II were prepared using [M + 5] labeled [13C, 15N4]-aminoguanidine, obtained from labeled thiourea. The overall yield for isotopically labeled II was 34% from [M + 3] labeled [13C, 15N2]-thiourea.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

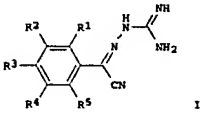
L4 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:631908 HCAPLUS
DOCUMENT NUMBER: 135:195578
TITLE: Process for preparing substituted benzoyl cyanide amidinohydrazones as intermediates for synthesis of 3,5-diamino-6-phenyl-1,2,4-triazines
INVENTOR(S): Nadaka, Vladimir; Lexner, Jael; Kaspi, Joseph
PATENT ASSIGNEE(S): Chemagis Ltd., Israel
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1127873 | A2 | 20010829 | EP 2001-103660 | 20010223 |
| EP 1127873 | A3 | 20030507 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| IL 134730 | A | 20031031 | IL 2000-134730 | 20000225 |
| CA 2337280 | A1 | 20010825 | CA 2001-2337280 | 20010215 |
| HU 200100740 | A2 | 20011128 | HU 2001-740 | 20010215 |
| US 2001025116 | A1 | 20010927 | US 2001-789634 | 20010222 |
| US 6329521 | B2 | 20011211 | | |

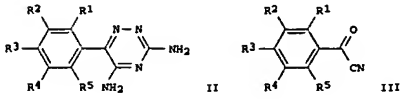




PRIORITY APPLN. INFO.: IL 2000-134730 A 20000225
OTHER SOURCE(S): CASREACT 135:195578; MARPAT 135:195578
GI



I



II III

AB The title compds. [I; R1-R5 = H, halo, alkyl, etc.], useful as intermediates for synthesis of 1,2,4-triazines II (active in the treatment of CNS disorders), were prepared by reacting the benzoyl cyanides III with aminoguanidine bicarbonate in a mixture of a water-soluble solvent and polyphosphoric acid. Thus, reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in the presence of polyphosphoric acid in MeCN afforded 2,3-dichlorobenzoyl cyanide amidinohydrazone which was then heated under reflux in PrOH to give 2,3-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

L4 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:507682 HCAPLUS
DOCUMENT NUMBER: 135:108812
TITLE: Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (lamotrigine)
INVENTOR(S): Radhakrishnan, Tarur Venkatasubramanian; Sasikumar, Thoovara Mohan; Srivastava, Anita Ranjan
PATENT ASSIGNEE(S): RPG Life Sciences Limited, India
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001049669 | A1 | 20010712 | WO 2000-IN1 | 20000103 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, | | | | |





SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| GB 2372988 | A | 20020911 | GB 2002-14791 | 20000103 |
| GB 2372988 | B | 20040407 | | |
| BR 2000016980 | A | 20021001 | BR 2000-16980 | 20000103 |
| DE 10085384 | T0 | 20021212 | DE 2000-10085384 | 20000103 |
| DE 10085384 | B4 | 20060614 | | |
| AU 763244 | B2 | 20030717 | AU 2000-44288 | 20000103 |
| IN 2002MN00829 | A | 20040313 | IN 2002-MN829 | 20020619 |
| US 6639072 | B1 | 20031028 | US 2002-149429 | 20020624 |

PRIORITY APPLN. INFO.: WO 2000-IN1 A 20000103
AB The title compound was prepared by hydrogenation of 2,3-Cl2C6H3NO2 in MeOH at 80 psi H pressure using Raney Ni catalyst at 30° to give 2,3-Cl2C6H3NH2 which was diazotized and converted to nitrile with CuCN/NaCN at 65-70°. The resulting 2,3-Cl2C6H3CN was hydrolyzed to give 2,3-Cl2C6H3CO2 which was converted to acid chloride at 80° with SOCl2. The 2,3-Cl2C6H3COCl was cyano-dehalogenated with CuCN/KI by refluxing in PhCl under an inert atmospheric and the product 2,3-Cl2C6H3COCN was condensed with aminoguanidine bicarbonate in PhMe in the presence of H2SO4 and p-MeC6H4SO3H at 100-120°, followed by in-situ cyclization of the Schiff base by refluxing with MeONa in MeOH. Crude lamotrigine is purified by recrystn. from MeOH.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:369058 HCAPLUS
DOCUMENT NUMBER: 136:14957
TITLE: Isolation of lamotrigine 2-N-glucuronide from guinea pig urine
AUTHOR(S): Yeh, Shih-Woei; Yu, Hsiu-Ying
CORPORATE SOURCE: School of Pharmacy, National Taiwan University, Taipei, 100, Taiwan
SOURCE: Chinese Pharmaceutical Journal (Taipei, Taiwan) (2001), 52(5), 241-249
CODEN: CPHJEP; ISSN: 1016-1015
PUBLISHER: Pharmaceutical Society of Republic of China
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lamotrigine (LT) is a novel anticonvulsant. Its major metabolite in human is 2-N-glucuronide (LT-2NG). In order to investigate the metabolic characteristics of LT in our laboratory, a reference standard of LT-2NG was required.
The purpose of this experiment was to isolate pure LT-2NG from the urine of LT-treated guinea pigs. The pooled urine of guinea pigs fed with LT was eluted with methanol through XAD-2 column. LT-2NG in the eluent was purified by semi-preparative HPLC equipped with a C8 column and a UV detector set at 267 nm. The mobile phase for HPLC was 0.01M ammonium acetate (pH 6.6) containing 12% of methanol. The isolated LT-2NG was confirmed by mass, 1H NMR and 13C NMR spectroscopic anal. The mol. ion 432.1, a downfield anomeric proton at 5.39 ppm, and an upfield shift (-6.9 ppm) of the triazine ring C-3 indicate attachment of the glucuronide to the N-2 of LT. These spectra were identical with the reported spectra of LT-2NG isolated from human urine.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT





L4 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:421116 HCAPLUS
DOCUMENT NUMBER: 133:60362
TITLE: An improved process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |
| | | | IN 1998-CA2171 | A 19981214 |
| | | | WO 1999-IB1955 | W 19991207 |

PRIORITY APPLN. INFO.:
AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) (I) useful as antiepileptic drug (no data) is prepared in a 3 step process. Thus, 2,3-dichlorobenzoylchloride was treated with cuprous cyanide in presence of acetonitrile and a solvent to produce 2,3-dichlorobenzoyl cyanide, further with aminoguanidine and cyclized to produce I.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:795469 HCAPLUS
DOCUMENT NUMBER: 132:26963
TITLE: Preparation of 1,2,4-triazine derivative, and its use as reference marker for testing purity and stability of lamotrigine
INVENTOR(S): Edmeades, Lorraine Mary; Griffith-Skinner, Nigel Arthur; Hill, Derek Anthony; Hill, Graham Thornton; Packham, Terrence William
PATENT ASSIGNEE(S): The Wellcome Foundation Limited, UK
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 963980 | A2 | 19991215 | EP 1999-200695 | 19990310 |
| EP 963980 | A3 | 20000531 | | |
| EP 963980 | B1 | 20020605 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| SG 85628 | A1 | 20020115 | SG 1999-1252 | 19990225 |
| MX 9902202 | A | 20000831 | MX 1999-2202 | 19990305 |
| KR 2000005611 | A | 20000125 | KR 1999-7632 | 19990309 |
| HR 990074 | A1 | 20001031 | HR 1999-74 | 19990309 |
| ZA 9901951 | A | 19990816 | ZA 1999-1951 | 19990310 |
| JP 2989189 | B2 | 19991213 | JP 1999-63792 | 19990310 |
| JP 2000009714 | A | 20000114 | | |
| NO 9901151 | A | 19991213 | NO 1999-1151 | 19990310 |
| CN 1238454 | A | 19991215 | CN 1999-103445 | 19990310 |
| AU 9920319 | A | 20000106 | AU 1999-20319 | 19990310 |
| TR 9900520 | A2 | 20000121 | TR 1999-520 | 19990310 |
| HU 9900592 | A2 | 20000428 | HU 1999-592 | 19990310 |
| BR 9900984 | A | 20000502 | BR 1999-984 | 19990310 |
| NZ 334590 | A | 20000728 | NZ 1999-334590 | 19990310 |
| CA 2265194 | C | 20001010 | CA 1999-2265194 | 19990310 |
| US 6333198 | B1 | 20011225 | US 1999-265670 | 19990310 |
| EP 1170588 | A1 | 20020109 | EP 2001-203376 | 19990310 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 218552 | T | 20020615 | AT 1999-200695 | 19990310 |
| PT 963980 | T | 20021031 | PT 1999-200695 | 19990310 |
| ES 2178342 | T3 | 20021216 | ES 1999-200695 | 19990310 |
| CN 1306210 | A | 20010801 | CN 2000-122208 | 20000725 |
| US 2002055177 | A1 | 20020509 | US 2001-940422 | 20010829 |
| NO 2003002753 | A | 19991213 | NO 2003-2753 | 20030617 |

PRIORITY APPLN. INFO.:
GB 1998-12413 A 19980610
EP 1999-200695 A3 19990310
US 1999-265670 A3 19990310

AB A method of testing the purity or stability to degradation of a sample of lamotrigine or a pharmaceutical dosage form comprising lamotrigine consists of assaying the sample for the presence of a compound selected from 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5-(4H)-one and N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide (I). A process for producing compound I, is also disclosed. Lamotrigine was treated with 2,3-dichlorobenzoyl chloride to give I. TLC-densitometry was used to determine I in lamotrigine tablets.

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:473716 HCAPLUS
DOCUMENT NUMBER: 127:81468
TITLE: Fluorophenyl-triazine and pyrimidine derivatives as compounds acting on the central nervous system
INVENTOR(S): Torrens Jover, Antoni; Frigola Constansa, Jordi
PATENT ASSIGNEE(S): Laboratorios Del Dr. Esteve, S.A., Spain; Torrens Jover, Antoni; Frigola Constansa, Jordi
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent



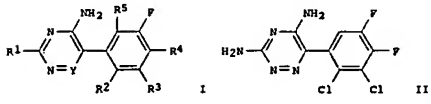


LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9720827 | A1 | 19970612 | WO 1996-EP5593 | 19961204 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| FR 2741879 | A1 | 19970606 | FR 1995-14354 | 19951205 |
| AU 9711943 | A | 19970627 | AU 1997-11943 | 19961204 |
| ES 2128960 | A1 | 19990516 | ES 1996-2667 | 19961205 |
| ES 2128960 | B1 | 20000116 | | |

PRIORITY APPLN. INFO.:
FR 1995-14354 A 19951205
WO 1996-EP5593 W 19961204

OTHER SOURCE(S): CASREACT 127:81468; MARPAT 127:81468
GI



AB Novel fluorophenyl-triazine and pyrimidine derivs. I and their physiol. acceptable salts are disclosed [wherein R1 = amino, 1-piperazinyl or 4-alkylpiperazin-1-yl, where alkyl = C1-4 chain, preferably Me; R2, R3, R4 = halo, preferably F or Cl; R5 = H or halo, preferably F or Cl; Y = N, CH]. A method for preparing the compds. is also disclosed, as are pharmaceutical compns. containing a pharmaceutically acceptable carrier and at least one such compound The compds. are CNS agents which act by inhibiting the release of glutamate. Examples include 13 syntheses, 1 standard formulation, and biol. data for 5 compds. For instance, 2,3-dichloro-4,5-difluorobenzoic acid (prepared in 3 steps) was converted to the acid chloride (99%) and then to the acyl cyanide (98%), and the latter was condensed with aminoguanidine bicarbonate and cyclized (31%) to give title compound II. In a test for prevention of hypoxic death in mice, II had an ED50 of 0.6 mg/kg i.p., vs. 1.2 mg/kg for lamotrigine.

L4 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:548552 HCAPLUS
DOCUMENT NUMBER: 125:195694
TITLE: Preparation of lamotrigine.
INVENTOR(S): Winter, Raymond Geoffrey; Sawyer, David Alan; Germain, Andrew
PATENT ASSIGNEE(S): Wellcome Foundation Limited, UK
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2





DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9620934 | A1 | 19960711 | WO 1995-GB3048 | 19951229 |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9643115 | A | 19960724 | AU 1996-43115 | 19951229 |
| EP 800520 | A1 | 19971015 | EP 1995-941817 | 19951229 |
| EP 800520 | B1 | 20020619 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV | | | | |
| HU 77346 | A2 | 19980330 | HU 1997-1867 | 19951229 |
| HU 224688 | B1 | 20051228 | | |
| JP 11501007 | T | 19990126 | JP 1995-520803 | 19951229 |
| RU 2145602 | C1 | 20000220 | RU 1997-112881 | 19951229 |
| AT 219487 | T | 20020715 | AT 1995-941817 | 19951229 |
| PT 800520 | T | 20021129 | PT 1995-941817 | 19951229 |
| ES 2177672 | T3 | 20021216 | ES 1995-941817 | 19951229 |
| FI 9702719 | A | 19970827 | FI 1997-2719 | 19970624 |
| US 5913345 | A | 19990615 | US 1997-836153 | 19970625 |

PRIORITY APPLN. INFO.:
GB 1994-26439 A 19941230
GB 1994-26447 A 19941230
WO 1995-GB3048 W 19951229

OTHER SOURCE(S): CASREACT 125:195694; MARPAT 125:195694
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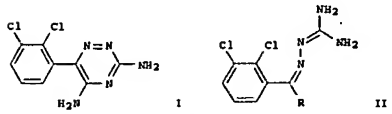

AB Lamotrigine (I) was prepared by irradiation of (II; R = CN, CONH2) with UV or visible radiation in an organic solvent, or, when R = CN, by heating. Thus, II (R = CN) was refluxed in 1-propanol under irradiation from a medium pressure Hg lamp for 8 h to give 73% lamotrigine.

L4 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:546365 HCAPLUS
DOCUMENT NUMBER: 125:195693
TITLE: Preparation of lamotrigine.
INVENTOR(S): Lee, Grehame Roy
PATENT ASSIGNEE(S): Wellcome Foundation Limited, UK
SOURCE: PCT Int. Appl., 25 pp.





CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9620935 | A1 | 19960711 | WO 1995-GB3049 | 19951229 |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9643116 | A | 19960724 | AU 1996-43116 | 19951229 |
| EP 800521 | A1 | 19971015 | EP 1995-941818 | 19951229 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV | | | | |
| HU 77347 | A2 | 19980330 | HU 1997-1875 | 19951229 |
| JP 11507011 | T | 19990622 | JP 1995-520618 | 19951229 |
| RU 2162081 | C2 | 20010120 | RU 1997-112921 | 19951229 |
| FI 9702720 | A | 19970827 | FI 1997-2720 | 19970624 |
| US 5925755 | A | 19990720 | US 1997-836152 | 19970625 |

PRIORITY APPLN. INFO.:
GB 1994-26448 A 19941230
WO 1995-GB3049 W 19951229

AB Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I), is prepared by treating 6-(2,3-dichlorophenyl)-5-chloro-3-thiomethyl-1,2,4-triazine (II) with NH3. Thus, II (preparation given) was heated with ethanolic NH3 in a sealed tube at 180° and 280 psi for 72 h to give I.

L4 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:128970 HCAPLUS
DOCUMENT NUMBER: 116:128970
TITLE: Preparation of 6-aminophenyl-3,5-diamino-1,2,4-triazines as neuroprotective agents
INVENTOR(S): Leach, Michael John; Nobbs, Malcolm Stuart
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 459829 | A1 | 19911204 | EP 1991-304962 | 19910531 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| ZA 9104158 | A | 19930301 | ZA 1991-4158 | 19910530 |
| CA 2043642 | A1 | 19911202 | CA 1991-2043642 | 19910531 |
| FI 9102622 | A | 19911202 | FI 1991-2622 | 19910531 |
| AU 9178099 | A | 19911205 | AU 1991-78099 | 19910531 |
| AU 630811 | B2 | 19921105 | | |
| HU 60726 | A2 | 19921028 | HU 1991-1827 | 19910531 |
| JP 06025193 | A | 19940201 | JP 1991-235335 | 19910531 |

PRIORITY APPLN. INFO.:
GB 1990-12312 A 19900601

OTHER SOURCE(S): MARPAT 116:128970

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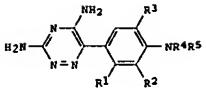

I

AB Title compds. (I; 1 of R1-R3 = Cl and the others = H or Cl; R4, R5 = H, alkyl) were prepared Thus, 2,5,3-Cl2(H2N)C6H2CO2H was converted in 3 steps to 2,3,5-Cl3C6H2COCN which was cyclocondensed with H2NC(:NH)NHNH2 and the product nitrated to give, after reduction, I (R1-R3 = Cl, R4 = R5 = H). The latter had IC50 of <10 μM against glutamate release from rat brain slices.

L4 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:112505 HCAPLUS
DOCUMENT NUMBER: 108:112505
TITLE: Preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate as an antiepileptic
INVENTOR(S): Sawyer, David Alan; Copp, Frederick Charles
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 247892 | A1 | 19871202 | EP 1987-304776 | 19870529 |
| EP 247892 | B1 | 19910424 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| DK 8702759 | A | 19871201 | DK 1987-2759 | 19870529 |
| DK 166278 | B | 19930329 | | |
| DK 166278 | C | 19930823 | | |
| FI 8702406 | A | 19871201 | FI 1987-2406 | 19870529 |
| FI 90770 | B | 19931215 | | |
| FI 90770 | C | 19940325 | | |
| AU 8773684 | A | 19871203 | AU 1987-73684 | 19870529 |
| AU 597982 | B2 | 19900614 | | |
| JP 62289570 | A | 19871216 | JP 1987-134772 | 19870529 |
| JP 07051571 | B | 19950605 | | |
| HU 45978 | A2 | 19880928 | HU 1987-2487 | 19870529 |
| HU 196769 | B | 19890130 | | |
| ZA 8703896 | A | 19890125 | ZA 1987-3896 | 19870529 |
| US 4847249 | A | 19890711 | US 1987-56136 | 19870529 |
| AT 62902 | T | 19910515 | AT 1987-304776 | 19870529 |
| CA 1286670 | C | 19910723 | CA 1987-538395 | 19870529 |
| IL 82710 | A | 19920115 | IL 1987-82710 | 19870529 |
| PRIORITY APPLN. INFO.: | | | GB 1986-13183 A | 19860530 |
| | | | EP 1987-304776 A | 19870529 |

AB The title compound (I.isethionate), useful as an anticonvulsant (no data),





was prepared by reaction of I with 2-hydroxyethanesulfonic acid (II) or by reaction of I salts with the anion of II. A 1.0 M solution of Na isethionate in H2O was passed through a column of IR 120 (H) ion exchange resin. I (preparation given) was added to the resulting II and the solution was filtered and evaporated Recrystn. from industrial methylated spirit gave 72% I.isethionate.

L4 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1985:542021 HCAPLUS
DOCUMENT NUMBER: 103:142021
TITLE: Triazine compounds having cardiovascular activity
INVENTOR(S): Allan, Geoffrey; Miller, Alastair Ainslie; Sawyer, David Alan
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 142306 | A2 | 19850522 | EP 1984-307374 | 19841026 |
| EP 142306 | A3 | 19861120 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| US 4649139 | A | 19870310 | US 1984-663682 | 19841022 |
| DK 8405121 | A | 19850428 | DK 1984-5121 | 19841026 |
| FI 8404212 | A | 19850428 | FI 1984-4212 | 19841026 |
| AU 8434758 | A | 19850509 | AU 1984-34758 | 19841026 |
| AU 564667 | B2 | 19870820 | | |
| JP 60109577 | A | 19850615 | JP 1984-225636 | 19841026 |
| DD 224033 | A5 | 19850626 | DD 1984-268757 | 19841026 |
| HU 36102 | A2 | 19850828 | HU 1984-4003 | 19841026 |
| HU 191566 | B | 19870330 | | |
| ES 537104 | A1 | 19860416 | ES 1984-537104 | 19841026 |
| ZA 8408388 | A | 19860625 | ZA 1984-8388 | 19841026 |
| SU 1371500 | A3 | 19880130 | SU 1984-3805251 | 19841026 |
| IL 73332 | A | 19880630 | IL 1984-73332 | 19841026 |
| PL 144899 | B1 | 19880730 | PL 1984-250213 | 19841026 |
| CA 1261328 | A1 | 19890926 | CA 1984-466473 | 19841026 |
| PRIORITY APPLN. INFO.: | | | GB 1983-28757 A | 19831027 |
| OTHER SOURCE(S): | MARPAT 103:142021 | | | |

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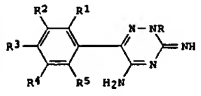

I

AB Tautomeric iminotriazinamines I [R = (un)substituted C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C3-10 cycloalkyl; R1-R5 = H, halogen, alkenyloxy, acyl, acyloxy, cyano, NO2, aryl, alkylthio, (un)subatituted alkyl,





alkenyl, alkynyl, alkoxy, amino; R1R2, R2R3, R3R4, R4R5 = CH:CHCH:CH] were prepared Thus, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine was alkylated with Me2CHI to give I-HI (R = Me2CH, R1 = R2 = Cl; R3-R5 = H) which was converted to the mesylate salt (II) (12% overall yield). II at 1 mg/kg i.v. to rats increased the amount of aconitine required to elicit ventricular arrhythmias by 490% compared with 84% for 1 mg/kg verapamil.

L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:89397 HCAPLUS
DOCUMENT NUMBER: 98:89397
TITLE: Substituted aromatic compounds
INVENTOR(S): Baxter, Martin G.; Elphick, Albert R.; Miller, Alistair A.; Sawyer, David A.
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Can., 26 pp. Division of Can. Appl. No. 353,081.
CODEN: CAXXA4
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CA 1133938 | A2 | 19821019 | CA 1981-373126 | 19810316 |
| CA 1112643 | A1 | 19811117 | CA 1980-353081 | 19800530 |
| US 4486354 | A | 19841204 | US 1981-308805 | 19811005 |
| AU 566870 | B2 | 19871105 | AU 1983-14051 | 19830428 |
| US 4602017 | A | 19860722 | US 1984-583286 | 19840227 |
| FI 8400888 | A | 19840306 | FI 1984-888 | 19840306 |
| FI 73203 | B | 19870529 | | |
| FI 73203 | C | 19870910 | | |
| PRIORITY APPLN. INFO.: | | | GB 1979-19257 A | 19790601 |
| | | | CA 1980-353081 A3 | 19800530 |
| | | | US 1980-154198 A1 | 19800529 |
| | | | FI 1980-1758 A | 19800530 |
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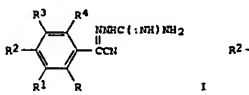

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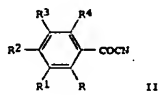

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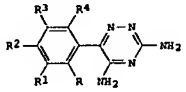

III





AB [(Cyanobenzylidene)amino]guanidines I (R-R4 = H, halo, alkyl, F3C; RR1 = HC:CHCH:CH, halobenzo, trifluoromethylbenzo, alkylbenzo) were prepared from the benzoyl cyanidea II and H2NNHC(:NH)NH2 and were useful as intermediates in the preparation of anticonvulsant triazines III. Thus, 2,3-Cl2C6H3COCl was treated with CuCN to give 2,3-Cl2C6H3COCN which was treated with H2NNHC(:NH)NH2 to give I (R = R1 = Cl, R2 = R3 = R4 = H), which was cyclized by KOH to give III (R = R2 = Cl, R2 = R3 = R4 = H) (IV). The anticonvulsant ED50 of IV was 2.4 mg/kg in the maximal electroshock test.

L4 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1981:208914 HCAPLUS
DOCUMENT NUMBER: 94:208914
TITLE: 1,2,4-Triazine derivatives, pharmaceutical compositions and intermediates utilized for their preparation
INVENTOR(S): Baxter, Martin George; Elphick, Albert Reginald; Miller, Alistair Ainslie; Sawyer, David Alan
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 21121 | A1 | 19810107 | EP 1980-103032 | 19800530 |
| EP 21121 | B1 | 19830511 | | |
| R: BE, CH, DE, FR, GB, LU, NL, SE | | | | |
| DK 8002338 | A | 19801202 | DK 1980-2338 | 19800530 |
| DK 153787 | B | 19880905 | | |
| DK 153787 | C | 19890116 | | |
| FI 8001758 | A | 19801202 | FI 1980-1758 | 19800530 |
| FI 67844 | B | 19850228 | | |
| FI 67844 | C | 19850610 | | |
| AU 8058906 | A | 19801204 | AU 1980-58906 | 19800530 |
| AU 530999 | B2 | 19830804 | | |
| JP 56025169 | A | 19810310 | JP 1980-71580 | 19800530 |
| JP 01044706 | B | 19890929 | | |
| ES 491998 | A1 | 19810516 | ES 1980-491998 | 19800530 |
| DD 151309 | A5 | 19811014 | DD 1980-221474 | 19800530 |
| ZA 8003250 | A | 19820127 | ZA 1980-3250 | 19800530 |
| AT 8002896 | A | 19820715 | AT 1980-2896 | 19800530 |
| AT 370097 | B | 19830225 | | |
| EP 59987 | A1 | 19820915 | EP 1982-102293 | 19800530 |
| EP 59987 | B1 | 19850814 | | |
| R: BE, CH, DE, FR, GB, LU, NL, SE | | | | |
| PL 124029 | B1 | 19821231 | PL 1980-224633 | 19800530 |
| HU 24621 | A2 | 19830328 | HU 1980-1364 | 19800530 |
| HU 182086 | B | 19831228 | | |
| IL 60201 | A | 19840531 | IL 1980-60201 | 19800530 |
| CS 234018 | B2 | 19850314 | CS 1980-3829 | 19800530 |
| SU 1055331 | A3 | 19831115 | SU 1980-2932704 | 19800602 |
| US 4486354 | A | 19841204 | US 1981-308805 | 19811005 |
| US 4602017 | A | 19860722 | US 1984-583286 | 19840227 |
| FI 8400888 | A | 19840306 | FI 1984-888 | 19840306 |

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| FI 73203 | B | 19870529 | | | |
| FI 73203 | C | 19870910 | | | |
| JP 61033163 | A | 19860217 | JP 1985-121370 | | 19850604 |
| JP 01044179 | B | 19890926 | | | |
| PRIORITY APPLN. INFO.: | | | GB 1979-19257 | A | 19790601 |
| | | | US 1980-154198 | A1 | 19800529 |
| | | | EP 1980-103032 | A | 19800530 |
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OTHER SOURCE(S): MARPAT 94:208914
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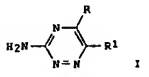

I

AB Triazines I (R = NH2, acylamino, aminomethyleneamino; R1 = substituted Ph) were prepared Thus, 2,3-Cl2C6H3I was Grignard carboxlated and the 2,3-Cl2C6H3CO2H converted to the chloride and treated with CuCN to give 2,3-Cl2C6H3COCN which was cyclized with aminoguanidine bicarbonate to I (R = NH2, R1 = 2,3-Cl2C6H3). The latter compound had an anticonvulsant ED50 of 2.4 mg/kg orally in mice.

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L6   1 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC   ICM A61K
CC   63-6 (Pharmaceuticals)
TI   Pharmaceutical composition containing lamotrigine particles of defined
     morphology
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ST   lamotrigine particle morphol seizure treatment
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IT   Alcohols, biological studies
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IT   Drug delivery systems
        (liqs., orsl; pharmaceutical composition containing lamotrigine particles of
        defined morphol. and excipients)
IT   Drug delivery systems
        (particles; pharmaceutical composition containing lamotrigine particles of
        defined morphol. and excipients)
IT   Acacia
     Anticonvulsants
     Chondrules
     Egg yolk
     Human
     Seizures
        (pharmaceutical composition containing lamotrigine particles of defined
morphol.
        and excipients)
IT   Alcohols, biological studies
     Bentonite, biological studies
     Carbohydrates, biological studies
     Casein, biological studies
     Gelatins, biological studies
     Kaolin, biological studies
     Polyoxyalkylenes, biological studies
     Tocopherols
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (pharmaceutical composition containing lamotrigine particles of defined
morphol.
        and excipients)
IT   Drug delivery systems
        (solids, orsl; pharmaceutical composition containing lamotrigine particles
of
        defined morphol. and excipients)
IT   Fats and Glyceridic oils, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (vegetable, hydrogenated; pharmaceutical composition containing lamotrigine
        particles of defined morphol. and excipients)
IT   Fats and Glyceridic oils, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (vegetable; pharmaceutical composition containing lamotrigine particles of
        defined morphol. and excipients)
IT   9003-01-4D, crosslinked
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        (Carbomer; pharmaceutical composition containing lamotrigine particles of
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IT   9003-39-8D, crosslinked
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
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IT   99-96-7D, alkyl esters
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        (Parabens; pharmaceutical composition containing lamotrigine particles of
        defined morphol. and excipients)
IT   7631-86-9, Colloidal silicon dioxide, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (colloidal; pharmaceutical composition containing lamotrigine particles of
        defined morphol. and excipients)
IT   9004-34-6, Cellulose, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (microcryst.; pharmaceutical composition containing lamotrigine particles of
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     biological studies   57-15-8, Chlorobutanol   57-48-7, Fructose,
     biological studies   57-50-1, Sucrose, biological studies   57-55-6,
     Propylene glycol, biological studies   57-88-5, Cholesterol, biological
     studies   60-00-4, Ethylenediamine tetraacetic acid, biological studies
     60-12-8, Phenethyl alcohol   63-42-3, Lactose   64-17-5, Ethyl alcohol,
     biological studies   64-19-7, Acetic acid, biological studies   69-65-8,
     Mannitol   72-17-3, Sodium lactate   77-92-9, Citric acid, biological
     studies   79-41-4D, Methacrylic acid, polymers   81-07-2, Saccharin
     87-69-4, biological studies   100-51-6, Benzyl alcohol, biological studies
     108-32-7, Propylene carbonate   121-54-0, Benzethonium chloride
     127-09-3, Sodium acetate   128-37-0, Butylated hydroxy toluene, biological
     studies   128-44-9, Sodium saccharin   471-34-1, Calcium carbonate,
     biological studies   526-95-4, Gluconic acid   527-07-1, Sodium gluconate
     532-32-1, Sodium benzoate   546-93-0, Magnesium carbonate   994-36-5,
     Sodium citrate   1309-48-4, Magnesium oxide, biological studies
     1327-43-1, Magnesium aluminum silicate   7447-40-7, Potassium chloride,
     biological studies   7631-90-5, Sodium bisulfite   7647-14-5, Sodium
     chloride, biological studies   7681-57-4, Sodium metabisulfite
     7758-87-4, Tribasic calcium phosphate   7778-18-9, Calcium sulfate
     7789-77-7, Dibasic calcium phosphate dihydrate   8013-17-0, Invert sugar
     8027-56-3, Liquid glucose   9000-30-0, Guar gum   9000-65-1, Tragacanth
     9000-69-5, Pectin   9002-89-5, Polyvinyl alcohol   9003-39-8, Povidone
     9004-32-4, Carboxymethylcellulose sodium   9004-53-9, Dextrin   9004-57-3,
     Ethyl cellulose   9004-62-0, Hydroxyethyl cellulose   9004-64-2,
     Hydroxypropyl cellulose   9004-65-3, Hydroxypropyl methylcellulose
     9004-67-5, Methylcellulose   9005-25-8, Starch, biological studies
     9005-32-7, Alginic acid   9005-37-2, Propylene glycol alginate
     9005-38-3, Sodium alginate   9050-04-8   9050-36-6, Maltodextrin
     9063-38-1, Sodium starch glycolate   11138-66-2, Xanthan gum   14807-96-6,
     Talc, biological studies   22839-47-0, Aspartame   25013-16-5, Butylated
     hydroxyanisole   25322-68-3, Polyethylene glycol   36653-82-4, Cetyl
     alcohol   39404-33-6, Dextrates   54182-62-6D, Polacrilin, potassium form
     74811-65-7, Croscarmellose sodium   84057-84-1, Lamotrigine
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (pharmaceutical composition containing lamotrigine particles of defined
morphol.
        and excipients)

ALL ANSWERS HAVE BEEN SCANNED

=> d his
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     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

     FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1             STRUCTURE UPLOADED
L2           3 S L1 SSS SAM
L3         128 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4          25 S LJ/P
              E US20050238724/PN,PRN,AN
L5           0 S E3/RN
L6           1 S E3

=> fil reg
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              78.55     257.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                 ENTRY    SESSION
CA SUBSCRIBER PRICE                             -19.50     -19.50

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
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STRUCTURE FILE UPDATES:     3 APR 2007  HIGHEST RN 929074-02-2
DICTIONARY FILE UPDATES:    3 APR 2007  HIGHEST RN 929074-02-2

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  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s 16
L7           0 US2005238724/PN

=> d his

     (FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

     FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1             STRUCTURE UPLOADED
L2           3 S L1 SSS SAM
L3         128 S L1 SSS FULL
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     FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4             25 S L3/P
                E US20050238724/PN,PRN,AN
L5              0 S E3/RN
L6              1 S E3

     FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7              0 S L6

=> fil hcaplus
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                             5.85     263.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)  SINCE FILE      TOTAL
                                              ENTRY    SESSION
CA SUBSCRIBER PRICE                             0.00     -19.50

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
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FILE COVERS 1907 - 4 Apr 2007  VOL 146 ISS 15
FILE LAST UPDATED: 3 Apr 2007  (20070403/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s lamotrigine/cn
   REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or PHITSTR) to directly view retrieved structures.



L9         1265 L8

=> s "3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine"
       6859857 "3"
       6355474 "5"
```





```
         35536 "DIAMINO"
             3 "DIAMINOS"
         35536 "DIAMINO"
                 ("DIAMINO" OR "DIAMINOS")
       3871969 "6"
       9105408 "2"
       6859857 "3"
         15829 "DICHLOROPHENYL"
      90786235 "1"
      91054408 "2"
       5555409 "4"
         41884 "TRIAZINE"
         10234 "TRIAZINES"
         44464 "TRIAZINE"
                 ("TRIAZINE" OR "TRIAZINES")
L10         27 "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"
                 ("3"(W)"5"(W)"DIAMINO"(W)"6"(W)"2"(W)"3"(W)"DICHLOROPHENYL"(W)
                 "1"(W)"2"(W)"4"(W)"TRIAZINE")

=> d scan l10 1-5
'1-5' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC    ICM  C07D253-06
      ICS  A61K031-53
CC    28-19 (Heterocyclic Compounds (More Than One Hetero Atom))
      Section cross-reference(s): 1, 63
TI    Preparation of 3,5-diamino-6-(
      2,3-dichlorophenyl)-1,2,
      4-triazine isethionate as an antiepileptic
ST    aminodichlorophenyltriazine isethionate prepn anticonvulsant; triazine
      diaminodichlorophenyl isethionate prepn anticonvulsant
IT    Anticonvulsants and Antiepileptics
         (diamino(dichlorophenyl)triazine.isethionate)
IT    6574-97-6, 2,3-Dichlorophenyl cyanide
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (cyclocondensation of, with aminoguanidine)
IT    2582-30-1, Aminoguanidine bicarbonate
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (cyclocondensation of, with dichlorophenyl cyanide)
IT    84057-84-1P
      RL: SPN (Synthetic preparation); PREP (Preparation)
         (preparation and conversion of, into isethionate salt)
IT    113170-86-8P
      RL: BAC (Biological activity or effector, except adverse); BSU (Biological
      study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
      BIOL (Biological study); PREP (Preparation); USES (Uses)
         (preparation of, as anticonvulsant)
IT    107-36-8, Isethionic acid
      RL: PROC (Process)
         (salt formation of, with diaminotriazine derivative)


The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
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CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
CLASS ------- IPC, NCL, ECLA, FTERM
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, CLASS

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
PHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
PHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field
codes.  For a list of the display field codes, enter HELP DFIELDS at
an arrow prompt (=>).  Examples of formats include: TI; TI,AU; BIB,ST;
TI,IND; TI,SO.  You may specify the format fields in any order and the
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to view a specified Accession Number.
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'IDE' IS NOT VALID HERE

To display more answers, enter the number of answers you would like to
see.  To end the display, enter "NONE", "N", "0", or "END".
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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):5

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC    ICM  A61K031-00
      ICS  C07D263-32
TI    Process for the preparation of 3,5-diamino-
      6-(2,3- dichlorophenyl)-1,
      2,4-triazine

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
CC    75 (Crystallography and Liquid Crystals)
TI    Lamotrigine dimethylformamide sesquisolvate

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
CC    25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
TI    Synthesis of 2,3-Dichlorobenzonitrile
ST    dichloroaniline diazotization; dichlorophenyldiazinium prepn Sandmeyer
      reaction; dichlorobenzonitrile prepn
IT    Substitution reaction
         (Sandmeyer; preparation of dichlorobenzonitrile via diazotization of
         dichloroaniline followed by Sandmeyer reaction)
IT    608-27-5, 2,3-Dichloroaniline
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (preparation of dichlorobenzonitrile via diazotization of dichloroaniline
         followed by Sandmeyer reaction)
IT    73260-77-2P
      RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
      (Reactant or reagent)
         (preparation of dichlorobenzonitrile via diazotization of dichloroaniline
         followed by Sandmeyer reaction)
IT    6574-97-6P, 2,3-Dichlorobenzonitrile
      RL: SPN (Synthetic preparation); PREP (Preparation)
         (preparation of dichlorobenzonitrile via diazotization of dichloroaniline
         followed by Sandmeyer reaction)

L10   27 ANSWERS   HCAPLUS  COPYRIGHT 2007 ACS on STN
IC    ICM  C07C281-18
CC    28-19 (Heterocyclic Compounds (More Than One Hetero Atom))
      Section cross-reference(s): 45
TI    Process for preparing 2-(2,3-dichlorophenyl)-2-
      (aminoguanidine)acetonitrile and a process for its cyclization into
      3,5-diamino-6-(2,3
      -dichlorophenyl)-1,2,4-
      triazine
ST    diaminodichlorophenyltriazine prepn cyclization
      dichlorophenylaminoguanidineacetonitrile
IT    Alcohols, uses
      RL: NUU (Other use, unclassified); USES (Uses)
         (aliphatic, solvents; in the cyclization of 2-(2,3-dichlorophenyl)-2-
         (aminoguanidine)acetonitrile into 3,5-
         diamino-6-(2,3-
         dichlorophenyl)-1,2,4-
         triazine)
IT    Condensation reaction catalysts
         (methanesulfonic acid; for the conversion of 2,3-dichlorobenzoyl
         cyanide with aminoguanidine bicarbonate in a non-aqueous medium to give
         2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)
IT    Condensation reaction
         (of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a
```

non-aqueous medium in the presence of methanesulfonic acid to give 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)
IT Cyclization
(of 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)
IT 75-75-2, Methanesulfonic acid
RL: CAT (Catalyst use); USES (Uses)
(condensation catalyst; in a process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile from 2,3-dichlorobenzoyl cyanide and aminoguanidine bicarbonate)
IT 2582-30-1, Aminoguanidine bicarbonate 77668-42-9, 2,3-Dichlorobenzoyl cyanide
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)
IT 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(in the condensation of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a non-aqueous medium in the presence of methanesulfonic acid to give 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile)
IT 84689-20-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)
IT 84057-84-1P, 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)
IT 64-17-5, Ethanol, uses 67-63-0, Isopropanol, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in the cyclization of 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine)

L10 27 ANSWERS HCAPLUS COPYRIGHT 2007 ACS on STN
CC 1-2 (Pharmacology)
TI Transplacental passage of lamotrigine in a human placental perfusion system in vitro and in maternal and cord blood in vivo
ST lamotrigine anticonvulsant bioavailability placenta perfusion pregnancy fetus epilepsy
IT Embryo, animal
(fetus; lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)
IT Anticonvulsants
Drug bioavailability





Epilepsy
Human
Perfusion
Placenta
Pregnancy
(lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)
IT Biological transport
(uptake; lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)
IT 84057-84-1, Lamotrigine
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lamotrigine transplacental passage in human placental perfusion system in vitro and in maternal and cord blood in vivo)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d his

(FILE 'HOME' ENTERED AT 16:55:13 ON 04 APR 2007)

FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
L1 STRUCTURE UPLOADED
L2 3 S L1 SSS SAM
L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4 25 S L3/P
E US20050238724/PN,PRN,AN
L5 0 S E3/RN
L6 1 S E3

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7 0 S L6

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
E LAMOTRIGINE+ALL/CT
S LAMOTRIGINE/CN

FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8 1 S LAMOTRIGINE/CN

FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9 1265 S L8
L10 27 S 3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

=> d l10 1-27 ibib abs

L10 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:365185 HCAPLUS
TITLE: Process for the preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Rawalnath, Sakhardande Rajiv; Kanji, Khatri Navin; Nilkanth, Firake Pandharinath; Vasant, Panchal Rajesh; Nagesh, Barekar Chandan; Madhukar, Mohite Dhanaji
PATENT ASSIGNEE(S): Saxena, Alok, India





SOURCE: Indian Pat. Appl.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| IN 2006MU00071 | A | 20060421 | IN 2006-MU71 | 20060117 |

PRIORITY APPLN. INFO.: IN 2006-MU71 20060117
AB There is disclosed an improved process for the preparation of 3,5- diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine which process comprises the step of reacting 2,3-dichlorobenzoylchloride with cuprous cyanide in presence of acetonitrile without the need of a co solvent to obtain dichlorbenzoyl cyanide, said dichlorobenzoyl cyanide is reacted with amino guanidine bicarbonate to produce a schiff;s base, which is cyclized in presence of aqueous potassium hydroxide to produce 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

L10 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:40805 HCAPLUS
TITLE: Crystal structure of lamotriginium hydrogen phthalate dimethylformamide solvate (1:1:1)
AUTHOR(S): Sridhar, Balasubramanian; Ravikumar, Krishnan
CORPORATE SOURCE: Lab. X-ray Crystallography, Indian Inst. Chemical Technology, Hyderabad, India
SOURCE: Molecular Crystals and Liquid Crystals (2006), 461, 131-141
CODEN: MCLCD8; ISSN: 1542-1406
PUBLISHER: Taylor & Francis, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title compound, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine-hydrogen phthalate-dimethylformamide, $C_9H_8N_5Cl_2^+ \cdot C_8H_5O_4^- \cdot C_3H_7NO$ (lamophthalate), crystallizes in the triclinic space group P1 with unit cell parameters a = 10.1587(6) Å, b = 11.3704(7) Å, c = 12.1976(7) Å, α = 110.797(1)°, β = 111.61(1)°, γ = 99.53(1)°, V = 1151.16(12) Å3, and Z = 2. The asym. unit comprises one lamotriginium cation, one hydrogen phthalate anion, and one DMF solvate. The dihedral angle between the two planar rings is 65.3(1)°. The expected proton transfer occurs at N2 of the triazine ring. Both O-H...O and N-H...O hydrogen bonding stabilizes the crystal structure.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1032885 HCAPLUS
TITLE: Lamotrigine dimethylformamide sesquisolvate
AUTHOR(S): Sridhar, Balasubramanian; Ravikumar, Krishnan
CORPORATE SOURCE: Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad, 500 007, India





SOURCE: Acta Crystallographica, Section E: Structure Reports Online (2006), E62(10), o4752-o4754
CODEN: ACSEBH; ISSN: 1600-5368
URL: http://journals.iucr.org/e/issues/2006/10/00/is2071/index.html
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB In the title compound, $C_9H_7N_5Cl_2 \cdot 1.5C_3H_7NO$, the asym. unit consists of two crystallog. independent lamotrigine [systematic name: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] and three DMF mols. In the crystal structure, N-H···N and N-H···O hydrogen bonds lead to the formation of R22(8) and R23(8) motifs.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:421792 HCAPLUS
DOCUMENT NUMBER: 142:430313
TITLE: Process for preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (Lamotrigine) via reaction of 2,3-dichlorobenzoyl chloride with cuprous cyanide and then with aminoguanidine bicarbonate followed by cyclization.
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): Torrent Pharmaceuticals Ltd., India
SOURCE: Indian, 12 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |
| US 6111101 | A | 20000829 | US 1999-456501 | 19991208 |

PRIORITY APPLN. INFO.: IN 1998-CA2171 A 19981214
WO 1999-IB1955 W 19991207
OTHER SOURCE(S): CASREACT 142:430313
AB Lamotrigine was prepared by reaction of 2,3-dichlorobenzoyl chloride with CuCN (1:1-2 molar ratio) in MeCN and a cosolvent to produce dichlorobenzoyl cyanide, reaction of the latter with aminoguanidine bicarbonate to produce the cyanoimine intermediate 2-[cyano(2,3-dichlorophenyl)methylene]hydrazinecarboximidamide, and cyclization of this in the presence of aqueous KOH at 80°-reflux.

L10 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1063399 HCAPLUS
DOCUMENT NUMBER: 143:326054
TITLE: Synthesis of 2,3-Dichlorobenzonitrile
AUTHOR(S): Deng, Hong; Liao, Qi; Zhou, Ying
CORPORATE SOURCE: Dept. of Chemistry, Central South Forestry University, Zhuzhou, Hunan Province, 412006, Peop. Rep. China
SOURCE: Jingxi Huagong Zhongjianti (2004), 34(5), 23-24
CODEN: JHZIAR; ISSN: 1009-9212
PUBLISHER: Jingxi Huagong Zhongjianti Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 143:326054
AB 2,3-Dichlorobenzonitrile was the important intermediate for synthesizing 2,3-dichlorobenzoic acid, which is the key intermediate for synthesizing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, the specific antiepileptic called Lamotrigine. 2,3-Dichlorobenzonitrile was synthesized from 2,3-dichloroaniline by diazo and Sandmeyer reaction. The yield was over 60%.

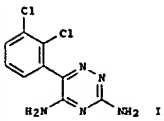
L10 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:421470 HCAPLUS
DOCUMENT NUMBER: 141:7119
TITLE: Preparation of crystalline lamotrigine and its monohydrate
INVENTOR(S): Manjunatha, Sulur G.; Kulkarni, Ashok Krishna; Kishore, Charugundia; Bokka, Ravisankar
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: Brit. UK Pat. Appl., 25 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| GB 2395483 | A | 20040526 | GB 2003-15608 | 20030703 |
| WO 2005003104 | A2 | 20050113 | WO 2004-IN186 | 20040628 |
| WO 2005003104 | A3 | 20050922 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, | | | | |





EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: GB 2003-15608 A 20030703
OTHER SOURCE(S): CASREACT 141:7119
GI



I

AB The invention relates to crystalline lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) (I) monohydrate and anhydrous lamotrigine. An improved process for manufacturing these products comprises reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in aqueous mineral acid, optionally together with a water miscible organic solvent, at 30-80° to produce the 2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (Schiff base) (II). The Schiff base II is further cyclized in aqueous organic solvent, e.g. alc. to produce pure lamotrigine of a pharmaceutically acceptable quality which on further drying at 45-50° under vacuum yields lamotrigine monohydrate, and/or on further drying at 100-110° yields anhydrous lamotrigine. The lamotrigine monohydrate or anhydrous lamotrigine thereby produced may then be brought into association with a pharmaceutically acceptable carrier for administration to a patient in need thereof.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:390214 HCAPLUS
DOCUMENT NUMBER: 140:391299
TITLE: Process for preparing 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile and a process for its cyclization into 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
INVENTOR(S): Dalmases Barjoan, Pere; Bessa Bellmunt, Jordi
PATENT ASSIGNEE(S): Laboratorios Vita, S.A., Spain
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004039767 | A1 | 20040513 | WO 2003-IB4763 | 20031027 |

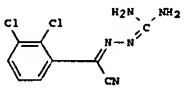




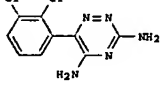
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| ES 2209639 | A1 | 20040616 | ES 2002-2502 | 20021031 |
| ES 2209639 | B1 | 20050801 | | |
| AU 2003272019 | A1 | 20040525 | AU 2003-272019 | 20031027 |
| EP 1556341 | A1 | 20050727 | EP 2003-753860 | 20031027 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2006052625 | A1 | 20060309 | US 2005-532397 | 20050422 |
| US 7179913 | B2 | 20070220 | | |
| NO 2005002574 | A | 20050527 | NO 2005-2574 | 20050527 |

PRIORITY APPLN. INFO.: ES 2002-2502 A 20021031
WO 2003-IB4763 W 20031027
OTHER SOURCE(S): CASREACT 140:391299
GI



I



II

AB A method for preparing the intermediate 2-(2,3-dichlorophenyl)-2-(aminoguanidine)acetonitrile (I; m.p. 180-183°) which comprises the condensation reaction of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in a non-aqueous medium in the presence of methanesulfonic acid, which produces good I yields and short reaction times. I is cyclized into 3,5-diamino-6-(2,3





-dichlorophenyl)-1,2,4-triazine (II; m.p. 217°) under reflux in an aliph alc. (e.g., ethanol) or alc.-water mixture
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:267313 HCAPLUS
DOCUMENT NUMBER: 140:303705
TITLE: Two-step process for the synthesis of high-purity 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine from 2,3-dichlorobenzoyl cyanide and aminoguanidine dimesylate
INVENTOR(S): Neu, Jozsef; Gizur, Tibor; Toerley, Jozsef; Csabai, Janos; Vegh, Ferenc; Kalvin, Peter; Tarkanyi, Gabor
PATENT ASSIGNEE(S): Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004026845 | A1 | 20040401 | WO 2003-HU72 | 20030918 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| HU 200203114 | A2 | 20040528 | HU 2002-3114 | 20020920 |
| CA 2498761 | A1 | 20040401 | CA 2003-2498761 | 20030918 |
| AU 2003267676 | A1 | 20040408 | AU 2003-267676 | 20030918 |
| EP 1539720 | A1 | 20050615 | EP 2003-748368 | 20030918 |
| EP 1539720 | B1 | 20061122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| AT 346051 | T | 20061215 | AT 2003-748368 | 20030918 |
| IN 2005KN00267 | A | 20060714 | IN 2005-KN267 | 20050224 |
| US 2006178511 | A1 | 20060810 | US 2005-528379 | 20051129 |

PRIORITY APPLN. INFO.: HU 2002-3114 A 20020920
WO 2003-HU72 W 20030918
OTHER SOURCE(S): CASREACT 140:303705
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB High-purity 3,5-diamino-6-(

2,3-dichlorophenyl)-1,2,
4-triazine (I; i.e., lamotrigine) is prepared by the
condensation reaction of 2,3-dichlorobenzoyl cyanide (II) with 1-2 mol
equivalent of an aminoguanidine salt (e.g., aminoguanidine dimesylate) in 3-6
mol equivalent of methanesulfonic acid, then the obtained adduct (III) is
transformed without isolation into the desired product by contacting it
with magnesium oxide, followed by crystallization of the product from an
appropriate organic solvent (e.g., acetone).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:159133 HCAPLUS
DOCUMENT NUMBER: 139:316547
TITLE: Transplacental passage of lamotrigine in a human placental perfusion system in vitro and in maternal and cord blood in vivo
AUTHOR(S): Myllynen, Paeivi K.; Pienimaeki, Paeivi K.; Vaehaekangas, Kirsi H.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Oulu, PO Box 5000, Oulu, FIN-90014, Finland
SOURCE: European Journal of Clinical Pharmacology (2003), 58(10), 677-682
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied transplacental passage of lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine; LTG) using an ex vivo human placental perfusion method and in vivo samples. Term placentas from healthy mothers without medications were perfused in a recirculating dual perfusion system. LTG (2.5 μg/mL, n = 4; 10 μg/mL, n = 4) and reference compound antipyrine (100 μg/mL) were added into the maternal circulation. The disappearance of drugs from the maternal circulation and appearance into the fetal circulation was followed every 15 min up to 2 h. Drug concns. were analyzed using high-performance liquid chromatog. In addition to human placental perfusions, we analyzed LTG concns. in maternal vein and cord blood samples after delivery from two epileptic mothers receiving LTG therapy during pregnancy. LTG was detectable in the fetal circulation at 15 min in all of the perfusions, indicating rapid transfer. Maternal and fetal concns. reached equilibrium at 60 min with both concns. used. The feto-maternal ratio was 1.26 ± 0.20 with 10 μg/mL LTG and 0.83 ± 0.41 with 2.5 μg/mL LTG at the end of the perfusion. The transfer of LTG from the maternal to the fetal compartment at 120 min was 28.9 ± 10.7% with 2.5 μg/mL LTG and 37.8 ± 3.2% with 10 μg/mL LTG (p > 0.05). In the serum samples from epileptic mothers, the cord blood maternal concentration ratio was 1.02 in one pair and 1.55 in the other. LTG crossed the placenta easily and rapidly, indicating that the maternal treatment leads to a considerable fetal exposure.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:76761 HCAPLUS
DOCUMENT NUMBER: 138:137336
TITLE: Method for producing lamotrigine from alpha-oxo-2,3-dichlorophenylacetamidinoaminoguanidino





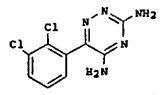
hydrazone by ring closure reaction
INVENTOR(S): Schneider, Geza; Gegoe, Csaba Lehel; Ondi, Levente; Mate, Attila Gergely; Luksa, Ferenc; Nyerges, Miklos; Gerzsai, Sandor
PATENT ASSIGNEE(S): Helm AG, Germany; CF Pharma Gyogyszergyarto Kft.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003008393 | A1 | 20030130 | WO 2002-EP7433 | 20020704 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10134980 | A1 | 20030213 | DE 2001-10134980 | 20010717 |
| DE 10134980 | C2 | 20030528 | | |
| EP 1311492 | A1 | 20030521 | EP 2002-758308 | 20020704 |
| EP 1311492 | B1 | 20040908 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE | | | | |
| CA 2417435 | C | 20040113 | CA 2002-2417435 | 20020704 |
| CA 2417435 | A1 | 20030130 | | |
| ES 2224074 | T3 | 20050301 | ES 2002-2758308 | 20020704 |
| US 2003191310 | A1 | 20031009 | US 2003-343225 | 20030515 |
| US 6683182 | B2 | 20040127 | | |

PRIORITY APPLN. INFO.: DE 2001-10134980 A 20010717
WO 2002-EP7433 W 20020704
OTHER SOURCE(S): CASREACT 138:137336; MARPAT 138:137336
GI







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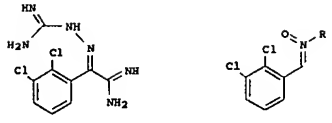

II III

AB The invention relates to a method for producing 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine [lamotrigine (I)], or its pharmaceutically acceptable salts, by ring closure reaction from α-oxo-2,3-dichlorophenylacetamidinoaminoguanidino hydrazone (II) or its salts. The preparation of II from N-oxides, III [R = linear, branched or cyclic (un)substituted alkyl, aryl, aralkyl], or their salts, are also described. Thus, I was prepared from 2,3-Cl2C6H3CH:N(O)Ph, via cyanation with NaCN, amination to the acetamidine hydrochloride, reaction with aminoguanine bicarbonate to give II·HCl, treatment with aqueous NaOH to give the free base, which is cyclized to I; cyclization of II·HCl gives I·HCl.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:775487 HCAPLUS
DOCUMENT NUMBER: 138:60875
TITLE: Development of a solid phase extraction protocol for the simultaneous determination of anthracene and its oxidation products in surface waters by reversed-phase HPLC
AUTHOR(S): Papadoyannis, I. N.; Zotou, A.; Samanidou, V. F.
CORPORATE SOURCE: Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki, GR-541 24, Greece
SOURCE: Journal of Liquid Chromatography & Related Technologies (2002), 25(17), 2635-2653
CODEN: JLCTFC; ISSN: 1082-6076
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A gradient reversed-phase HPLC (RP-HPLC) method for the simultaneous determination





of anthracene, anthraquinone, and 1-hydroxyanthraquinone, with photodiode array detection at 250 nm, was developed. The separation was achieved on a Kromasil 100 C8 5 μm 250 × 4 mm column, applying a 10-min linear gradient elution starting with 85% methanol and 15% 0.05M ammonium acetate and ending up with 95% of methanol and 5% 0.05M ammonium acetate, at a flow-rate 0.7 mL/min, using 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) as internal standard
Calibration curves were rectilinear for 0.1-3.0 ng anthracene, 0.1-10.0 ng anthraquinone, and 0.5-20.0 ng 1-hydroxyanthraquinone, when 10 μL was injected. The detection limits were 0.05 ng injected on-column for anthracene and anthraquinone and 0.3 ng on-column for 1-hydroxyanthraquinone. The average intra- and inter-day RSDs for injection precision (in terms of peak area) were 1.95 and 3.62%, resp. The method was applied to the anal. of river and lake waters. A protocol, combining solid phase extraction (SPE) with sonication of matrix with sorbent, was developed for enhancement of recovery. The proposed protocol was chosen among other studied, after optimization of each step. Mean recoveries were 50% for anthracene, 71% for anthraquinone, and 105% for 1-hydroxy anthraquinone.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:435163 HCAPLUS
DOCUMENT NUMBER: 133:160143
TITLE: Evidence that DHPG-induced nociception depends on glutamate release from primary afferent C-fibres
AUTHOR(S): Lefebvre, Celeste; Fisher, Kim; Cahill, Catherine M.; Coderre, Terence J.
CORPORATE SOURCE: Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: NeuroReport (2000), 11(8), 1631-1635
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors examined whether enhanced glutamate release contributes to the expression of persistent spontaneous nociceptive behaviors (SNBs) in rats induced by intrathecal (i.t.) administration of the selective group I mGluR agonist, (RS)-3,5-dihydroxyphenylglycine ((RS)-DHPG). Pretreatment with drugs that have been shown to inhibit glutamate release, including a group II metabotropic glutamate receptor (mGluR) agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate ((2R,4R)-APDC), a group III mGluR agonist L-2-amino-4-phosphonobutyrate (L-AP4), or the use-dependent sodium channel blockers 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) and 2-amino-6-trifluoromethoxybenzothiazole (riluzole), produced dose-dependent reduns. in (RS)-DHPG-induced SNBs. The authors have also shown that incubation of rat lumbar spinal cord slices with (RS)-DHPG potentiates 4-aminopyridine-evoked (4-AP) release of glutamate. Furthermore, the authors found that destruction of unmyelinated primary afferent C-fibers by neonatal capsaicin treatment significantly reduced (RS)-DHPG-induced SNBs in adult rats. Together, these results suggest that (RS)-DHPG-induced nociception is dependent on spinal glutamate release, probably from primary afferent C-fibers.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:421116 HCAPLUS
DOCUMENT NUMBER: 133:60362
TITLE: An improved process for preparation of 3, 5-diamino-6-(2, 3-dichlorophenyl)-1, 2,4-triazine
INVENTOR(S): Vyas, Sharad Kumar
PATENT ASSIGNEE(S): India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000035888 | A1 | 20000622 | WO 1999-IB1955 | 19991207 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| IN 183150 | A1 | 19990925 | IN 1998-CA2171 | 19981214 |
| CA 2334937 | A1 | 20000622 | CA 1999-2334937 | 19991207 |
| CA 2334937 | C | 20040921 | | |
| AU 2000012924 | A | 20000703 | AU 2000-12924 | 19991207 |
| EP 1140872 | A1 | 20011010 | EP 1999-956293 | 19991207 |
| EP 1140872 | B1 | 20030917 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AT 250041 | T | 20031015 | AT 1999-956293 | 19991207 |
| RU 2231526 | C2 | 20040627 | RU 2001-115698 | 19991207 |

PRIORITY APPLN. INFO.: IN 1998-CA2171 A 19981214
WO 1999-IB1955 W 19991207

AB 3,5-Diamino-6-(2, 3-dichlorophenyl)-1,2,4-triazine (lamotrigine) (I) useful as antiepileptic drug (no data) is prepared in a 3 step process. Thus, 2,3-dichlorobenzoylchloride was treated with cuprous cyanide in presence of acetonitrile and a solvent to produce 2,3-dichlorobenzoyl cyanide, further with aminoguanidine and cyclized to produce I.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:12098 HCAPLUS
DOCUMENT NUMBER: 132:130210
TITLE: Structure of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate solvate (lamotrigine isethionate)
AUTHOR(S): Potter, Brian; Palmer, Rex A.; Withnall, Robert;





Leach, Michael J.; Chowdhry, Babur Z.
CORPORATE SOURCE: Department of Crystallography, Birkbeck College, University of London, London, WC1E 7HX, UK
SOURCE: Journal of Chemical Crystallography (1999), 29(6), 701-706
CODEN: JCCYEV; ISSN: 1074-1542
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The crystal and mol. structure of lamotrigine isethionate was determined by direct methods. The compound crystallizes in the tetragonal space group I41/a, with a 19.684(5), c 16.557(5) Å; Z = 16, dc = 1.579; R = 0.0532, Rw = 0.1317 for 2041 reflections. Atomic coordinates are given. The isethionate moiety forms multiple H bonds to the lamotrigine nucleus, three from one isethionate, two from a symmetry related isethionate and a further two from two different symmetry related mols. Protonation of N(2') in the triazine ring, not observed in the native lamotrigine structure is presumably associated with the interaction of the isethionate moiety. Both rings in the lamotrigine moiety are essentially planar, with a dihedral angle of 66.08(7)° compared to 80.70° in native lamotrigine. The connecting bond length C(1)-C(6') 1.493(3) Å also correlates well with values in related compds. (1.480(3) Å) in the native structures.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:682978 HCAPLUS
DOCUMENT NUMBER: 132:98214
TITLE: Detection of the principal synthetic route indicative impurity in lamotrigine
AUTHOR(S): Ashton, D. S.; Ray, A. D.; Valko, K.
CORPORATE SOURCE: School of Pharmacy, University of London, London, UK
SOURCE: International Journal of Pharmaceutics (1999), 189(2), 241-248
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An anal. method has been developed for the detection of trace amts. of the principal synthetic route indicative impurity in lamotrigine (3, 5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine). A sample extract was preconcd. by normal-phase high-performance liquid chromatog. (HPLC) and analyzed by subsequent online reversed-phase HPLC-thermospray mass spectrometry (TSP-MS). During the sample extraction and concentration step, carried out by semipreparative normal-phase chromatog., the preliminary separation of the impurity from the lamotrigine takes place. The organic solvent (dichloroethane-methanol, 90:10, volume/volume) is evaporated from the collected fraction and the material is redissolved in a smaller volume of the reversed-phase mobile phase. The collected fraction is then subjected to reversed-phase HPLC-TSP-MS. The influence of an ultrasonic extraction step has been examined. When the method was applied to lamotrigine tablets, a shake flask partitioning step using 1 mg/mL EDTA in water-dichloroethane was used instead of the ultrasonic extraction. Detection limit and recovery measurements showed that the route indicative impurity formed during the synthesis could be detected in the 50-100 ppb (weight/weight)





range.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:289572 HCAPLUS
DOCUMENT NUMBER: 127:636
TITLE: A calcium antagonistic effect of the new antiepileptic drug lamotrigine
AUTHOR(S): v. Wegerer, J.; Hesslinger, B.; Berger, M.; Walden, J.
CORPORATE SOURCE: Universitaet Freiburg, Abt. Psychiatrie und Psychotherapie, Heuptstr. 5, 79104, Freiburg, Germany
SOURCE: European Neuropsychopharmacology (1997), 7(2), 77-81
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The new antiepileptic drug lamotrigine (LTG; 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) has been shown to be effective in the treatment of focal epilepsies with or without secondary generalization. Furthermore, some case reports indicate an efficacy in the treatment of bipolar affective disorders. It has been suggested that the main mechanism of action of LTG is the inhibition of glutamate release through blockade of voltage sensitive sodium channels and stabilization of the neuronal membrane. Since some antidepressant drugs and the antiepileptic substance carbamazepine have calcium antagonistic properties, which may be of significance in the pathophysiol. of epilepsies and affective disorders, the interaction of lamotrigine with carbamazepine and the organic calcium channel blocker verapamil was analyzed in the low Mg2+-induced model epilepsy which has been shown to be suppressed specifically by organic calcium antagonists. Lamotrigine reduced the frequency of occurrence of low-magnesium induced field potentials in CA1 and CA3 areas of the hippocampus slice preparation (guinea pigs) in a dose-dependent manner. The subthreshold concns. which yielded no effect were 1 μmol/L for lamotrigine, 10 μmol/L for carbamazepine and 2 μmol/L for verapamil. Combinations of these subthreshold concns. elicited a reduction in the repetition rate of field potentials. The results indicate that lamotrigine behaves additive with verapamil and carbamazepine what can be due to a common action on the same subtype of calcium channels. It can be assumed that lamotrigine may have besides its action on high-frequency sodium dependent action potentials also effects on calcium channels.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:288924 HCAPLUS
DOCUMENT NUMBER: 126:312094
TITLE: Effects of lamotrigine on brain nitrite and cGMP levels during focal cerebral ischemia in rats
AUTHOR(S): Balkan, S.; Ozben, T.; Balkan, E.; Oguz, N.; Serteser, M.; Gumuslu, S.
CORPORATE SOURCE: Department of Neurology, School of Medicine, Akdeniz University, Antalya, 07070, Turk.
SOURCE: Acta Neurologica Scandinavica (1997), 95(3), 140-146
CODEN: ANRSAS; ISSN: 0001-6314
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal





LANGUAGE: English
AB Glutamate receptor antagonists are protective in animal models of focal cerebral ischemia. Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an anticonvulsant drug that blocks voltage-gated sodium channels and inhibits the ischemia-induced release of glutamate. Expts. in primary neuronal cultures implicate nitric oxide (NO) as a mediator of glutamatergic neurotoxicity acting via N-Methyl-D-Asparate (NMDA) receptors. The effect of glutamate release inhibitor, lamotrigine, upon NO and cGMP production has been examined in focal cerebral ischemia in rats. Focal cerebral ischemia was produced by the permanent occlusion of right middle cerebral artery (MCA) in urethane anesthetized rats. A number of indicators of brain NO production (nitrite, cGMP) were determined in ipsilateral and contralateral cerebral cortex and cerebellum after 0, 10, 60 min of focal cerebral ischemia. The same parameters were measured in rats treated with Lamotrigine (20 mg/kg, i.p.) 30 min before or just after the occlusion of the right MCA.

L10 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:546365 HCAPLUS
DOCUMENT NUMBER: 125:195693
TITLE: Preparation of lamotrigine.
INVENTOR(S): Lee, Grahame Roy
PATENT ASSIGNEE(S): Wellcome Foundation Limited, UK
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9620935 | A1 | 19960711 | WO 1995-GB3049 | 19951229 |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9643116 | A | 19960724 | AU 1996-43116 | 19951229 |
| EP 800521 | A1 | 19971015 | EP 1995-941818 | 19951229 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV | | | | |
| HU 77347 | A2 | 19980330 | HU 1997-1875 | 19951229 |
| JP 11507011 | T | 19990622 | JP 1995-520618 | 19951229 |
| RU 2162081 | C2 | 20010120 | RU 1997-112921 | 19951229 |
| FI 9702720 | A | 19970827 | FI 1997-2720 | 19970624 |
| US 5925755 | A | 19990720 | US 1997-836152 | 19970625 |

PRIORITY APPLN. INFO.: GB 1994-26448 A 19941230
WO 1995-GB3049 W 19951229

AB Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I), is prepared by treating 6-(2,3-dichlorophenyl)-5-chloro-3-thiomethyl-1,2,4-triazine (II) with NH3. Thus, II (preparation given) was heated with ethanolic NH3 in a sealed tube at 180° and 280 psi for 72 h to give I.

L10 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:186621 HCAPLUS
DOCUMENT NUMBER: 124:278888
TITLE: Inhibition of morphine withdrawal by lamotrigine: involvement of nitric oxide
AUTHOR(S): Lizasoain, Ignacio; Leza, Juan C.; Cuellar, Beatriz; Moro, Maria A.; Lorenzo, Pedro
CORPORATE SOURCE: Departamento de Farmacologia, Facultad de Medicina, Universidad Complutense de Madrid, Avenida Complutense s/n, Madrid, 28040, Spain
SOURCE: European Journal of Pharmacology (1996), 299(1-3), 41-5
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied the effects of lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine], a new antiepileptic compound, on naloxone-precipitated morphine withdrawal in mice. Pretreatment with lamotrigine (5-100 mg/kg, s.c.) reversed in a dose-dependent way the withdrawal-induced increase in cerebellar Ca2+-dependent nitric oxide (NO) synthase activity and reduced the number of escape jumps and other motor symptoms of abstinence, at doses that did not modify locomotor activity (25-50 mg/kg). Pretreatment with the NMDA receptor antagonist MK-801 [(+)-5-methyl-10,11-dihydroxy-5H-dibenzo[a,d]cyclohepten-5,10-imine; dizocilpine] (0.1-0.3 mg/kg, s.c.) also reversed the increase in cerebellar Ca2+-dependent NO synthase activity. However, although MK-801 reduced the number of escape jumps and other motor symptoms of abstinence, its effects were not clearly dose-dependent. Furthermore, the highest dose of MK-801 tested (0.3 mg/kg) caused an impairment of the locomotor behavior in naive mice. Thus, lamotrigine may represent a new and useful agent for the treatment of opiate abstinence.

L10 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:499316 HCAPLUS
DOCUMENT NUMBER: 123:699
TITLE: Cerebroprotective effect of lamotrigine after focal ischemia in rats
AUTHOR(S): Smith, Stuart E.; Meldrum, Brian S.
CORPORATE SOURCE: Department of Neurology, Institute of Psychiatry, Denmark Hill, SE5 8AF, UK
SOURCE: Stroke (1995), 26(1), 117-22
CODEN: SJCCA7; ISSN: 0039-2499
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamate receptor antagonists are protective in animal models of focal cerebral ischemia. Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine) is an anticonvulsant drug that blocks voltage-gated sodium channels and inhibits the ischemia-induced release of glutamate. The cerebroprotective effect of lamotrigine (as the isethionate salt) after middle cerebral artery occlusion was described in rats. Neurol. deficit and infarct volume (visualized by the lack of reduction of 2,3,5-triphenyltetrazolium chloride) 24 h after permanent left middle cerebral artery occlusion were studied in Fischer rats (n=8 per group per dose). Lamotrigine at 20 mg/kg i.v. over





10 min administered immediately after middle cerebral artery occlusion reduced total infarct volume by 31% and cortical infarct volume by 52%. Lamotrigine at 8 mg/kg i.v. over 10 min reduced cortical infarct volume by 38%. Lamotrigine at 50 mg/kg i.v. for 10 min was not cerebroprotective and induced a decrease of 29±15 mm Hg in mean arterial blood pressure (P<.05, n=8). The optimum dose of lamotrigine (20 mg/kg i.v. over 10 min) when administered with a 1-h delay after middle cerebral artery occlusion reduced cortical infarct volume by 41%. Lamotrigine (20 mg/kg i.v. over 10 min) with a 2-h delay after middle cerebral artery occlusion was ineffective. Neurol. deficits after 24 h were improved after immediate treatment with lamotrigine at 20 mg/kg i.v. over 10 min. The cerebroprotective effect of lamotrigine in rats is limited to a narrow dose range between 8 and 20 mg/kg. Lamotrigine or analogous compds. may be useful when given shortly after the onset of stroke.

L10 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:663729 HCAPLUS
DOCUMENT NUMBER: 121:263729
TITLE: Use of triazine compounds for the treatment of memory and learning disorders
INVENTOR(S): Baxter, Martin George
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9421260 | A1 | 19940929 | WO 1994-GB559 | 19940318 |
| W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9462176 | A | 19941011 | AU 1994-62176 | 19940318 |
| ZA 9401938 | A | 19950918 | ZA 1994-1938 | 19940318 |
| EP 689439 | A1 | 19960103 | EP 1994-909263 | 19940318 |
| EP 689439 | B1 | 20010124 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 08507782 | T | 19960820 | JP 1994-520807 | 19940318 |
| IL 109034 | A | 19981206 | IL 1994-109034 | 19940318 |
| AT 198831 | T | 20010215 | AT 1994-909263 | 19940318 |
| ES 2153854 | T3 | 20010316 | ES 1994-909263 | 19940318 |
| PT 689439 | T | 20010531 | PT 1994-909263 | 19940318 |
| US 5866597 | A | 19990202 | US 1997-900868 | 19970725 |
| GR 3035528 | T3 | 20010629 | GR 2001-400367 | 20010308 |
| PRIORITY APPLN. INFO.: | | | GB 1993-5693 A | 19930319 |
| | | | WO 1994-GB559 W | 19940318 |
| | | | US 1996-535140 B1 | 19960328 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I) and its pharmaceutically acceptable acid addition salts can be used to treat impaired memory and learning disorders. Therapeutic effects of I were demonstrated in a scopolamine-induced mouse model of memory deficit and compared with those of ondansetron HCl and piracetam. A tablet containing 150 mg I was also formulated.





L10 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:663728 HCAPLUS
DOCUMENT NUMBER: 121:263728
TITLE: Use of triazine compounds as anxiolytics
INVENTOR(S): Critchley, Martyn Alan Edwin
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9421261 | A1 | 19940929 | WO 1994-GB560 | 19940318 |
| W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9462177 | A | 19941011 | AU 1994-62177 | 19940318 |
| ZA 9401939 | A | 19950918 | ZA 1994-1939 | 19940318 |
| EP 689440 | A1 | 19960103 | EP 1994-909264 | 19940318 |
| EP 689440 | B1 | 20000531 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 08507783 | T | 19960820 | JP 1994-520808 | 19940318 |
| JP 3633618 | B2 | 20050330 | | |
| AT 193446 | T | 20000615 | AT 1994-909264 | 19940318 |
| ES 2147232 | T3 | 20000901 | ES 1994-909264 | 19940318 |
| PT 689440 | T | 20001031 | PT 1994-909264 | 19940318 |
| US 5658905 | A | 19970819 | US 1995-535139 | 19950918 |
| GR 3033941 | T3 | 20001130 | GR 2000-401626 | 20000712 |
| PRIORITY APPLN. INFO.: | | | GB 1993-5692 A | 19930319 |
| | | | WO 1994-GB560 W | 19940318 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (I) and its pharmaceutically acceptable acid addition salts can be used to treat anxiety and anxiety disorders. For example, an anxiolytic effect of I-isethionate was demonstrated with Vogel conflict model in rats. A tablet containing 150 mg I was also formulated.

L10 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:124865 HCAPLUS
DOCUMENT NUMBER: 120:124865
TITLE: Use of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine isethionate for the treatment and prevention of dependence on, tolerance to, and sensitization to drugs
INVENTOR(S): Nakamura-Craig, Meire
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1





PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9325207 | A1 | 19931223 | WO 1993-GB1243 | 19930611 |
| W: AU, CA, CZ, GB, JP, KR, NO, NZ, PL, RU, SK, UA, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9343452 | A | 19940104 | AU 1993-43452 | 19930611 |
| AU 668729 | B2 | 19960319 | | |
| EP 644763 | A1 | 19950329 | EP 1993-913346 | 19930611 |
| EP 644763 | B1 | 19970122 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| GB 2282326 | A | 19950405 | GB 1994-23697 | 19930611 |
| JP 07507790 | T | 19950831 | JP 1993-501281 | 19930611 |
| AT 147980 | T | 19970215 | AT 1993-913346 | 19930611 |
| ES 2097516 | T3 | 19970401 | ES 1993-913346 | 19930611 |
| CZ 284061 | B6 | 19980812 | CZ 1994-3128 | 19930611 |
| IL 105986 | A | 19981206 | IL 1993-105986 | 19930611 |
| SK 279730 | B6 | 19990211 | SK 1994-1534 | 19930611 |
| HR 930964 | B1 | 20000630 | HR 1993-964 | 19930611 |
| JP 3439211 | B2 | 20030825 | JP 1994-501281 | 19930611 |
| US 5801171 | A | 19980901 | US 1994-347480 | 19941206 |
| NO 9404790 | A | 19941209 | NO 1994-4790 | 19941209 |
| PRIORITY APPLN. INFO.: | | | GB 1992-12495 A | 19920612 |
| | | | GB 1993-8654 A | 19930427 |
| | | | WO 1993-GB1243 A | 19930611 |

AB 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4,-triazine (I) and its pharmaceutically and veterinarily acceptable salts (especially the ethionate) have activity in (a) preventing or reducing dependence on, and (b) preventing or reducing tolerance or reverse tolerance to, a dependence-inducing agent such as an opioid, a central nervous system depressant, a psychostimulant, or nicotine. Thus, I (5 mg/kg orally twice a day during morphine habituation) attenuated the development of morphine tolerance in rats without affecting the analgesic effect of morphine in the tail-flick test.

L10 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:617428 HCAPLUS
DOCUMENT NUMBER: 119:217428
TITLE: Use of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine for the treatment of pain and edema
INVENTOR(S): Nakamura-Craig, Meire; Leach, Michael John
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9316700 | A1 | 19930902 | WO 1993-GB341 | 19930218 |
| W: AU, CA, GB, JP, KR, NZ, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |

| | | | | | |
|---|---|---|---|---|---|
| AU 9335092 | A | 19930913 | AU 1993-35092 | | 19930218 |
| AU 684711 | B2 | 19980108 | | | |
| EP 626851 | A1 | 19941207 | EP 1993-904225 | | 19930218 |
| EP 626851 | B1 | 20010822 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | | |
| JP 07503968 | T | 19950427 | JP 1993-514628 | | 19930218 |
| JP 3713271 | B2 | 20051109 | | | |
| IL 104775 | A | 19970218 | IL 1993-104775 | | 19930218 |
| AT 204476 | T | 20010915 | AT 1993-904225 | | 19930218 |
| ES 2162813 | T3 | 20020116 | ES 1993-904225 | | 19930218 |
| PT 626851 | T | 20020228 | PT 1993-904225 | | 19930218 |
| CA 2129043 | C | 20040127 | CA 1993-2129043 | | 19930218 |
| GB 2277265 | A | 19941026 | GB 1994-14348 | | 19940715 |
| GB 2277265 | B | 19960110 | | | |
| US 5712277 | A | 19980127 | US 1996-680111 | | 19960715 |
| GR 3036958 | T3 | 20020131 | GR 2001-401827 | | 20011022 |
| PRIORITY APPLN. INFO.: | | | GB 1992-3483 | A | 19920219 |
| | | | WO 1993-GB341 | A | 19930218 |
| | | | US 1994-284497 | A1 | 19940804 |

AB The title compound (I) is useful in medicaments for the prevention or treatment of pain or edema. A tablet formulation containing I is given. I was tested in rats.

L10 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:126056 HCAPLUS
DOCUMENT NUMBER: 110:126056
TITLE: Structure of lamotrigine methanol solvate: 3 ,5-diamino-6-(2 ,3-dichlorophenyl)-1, 2,4-triazine-methanol, a novel anticonvulsant drug
AUTHOR(S): Janes, Robert W.; Lisgarten, John N.; Palmer, Rex A.
CORPORATE SOURCE: Birkbeck Coll., Univ. London, London, WC1E 7HX, UK
SOURCE: Acta Crystallographica, Section C: Crystal Structure Communications (1989), C45(1), 129-32
CODEN: ACSCEE; ISSN: 0108-2701
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title compound is monoclinic, space group P21/n, with a 15.456(3), b 11.736(2), c 7.300(3) Å, and β 94.417(3)°; Z = 4 for dc = 1.449. The final R = 0.055 for 2444 reflections. Atomic coordinates are given. The Ph and triazine aromatic rings make a dihedral angle of 80.6(9)° with each other. The bond linking the 2 rings is 1.480(3) Å. The structure is stabilized by a network of H bonds involving amino and ring N atoms, one of the Cl atoms, and the MeOH of crystallization

L10 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:112505 HCAPLUS
DOCUMENT NUMBER: 108:112505
TITLE: Preparation of 3,5-diamino -6-(2,3-dichlorophenyl)-1,2, 4-triazine isethionate as an antiepileptic
INVENTOR(S): Sawyer, David Alan; Copp, Frederick Charles
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent





LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 247892 | A1 | 19871202 | EP 1987-304776 | 19870529 |
| EP 247892 | B1 | 19910424 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| DK 8702759 | A | 19871201 | DK 1987-2759 | 19870529 |
| DK 166278 | B | 19930329 | | |
| DK 166278 | C | 19930823 | | |
| FI 8702406 | A | 19871201 | FI 1987-2406 | 19870529 |
| FI 90770 | B | 19931215 | | |
| FI 90770 | C | 19940325 | | |
| AU 8773684 | A | 19871203 | AU 1987-73684 | 19870529 |
| AU 597982 | B2 | 19900614 | | |
| JP 62289570 | A | 19871216 | JP 1987-134772 | 19870529 |
| JP 07051571 | B | 19950605 | | |
| HU 45978 | A2 | 19880928 | HU 1987-2487 | 19870529 |
| HU 196769 | B | 19890130 | | |
| ZA 8703696 | A | 19890125 | ZA 1987-3696 | 19870529 |
| US 4847249 | A | 19890711 | US 1987-56136 | 19870529 |
| AT 62902 | T | 19910515 | AT 1987-304776 | 19870529 |
| CA 1286670 | C | 19910723 | CA 1987-538395 | 19870529 |
| IL 82710 | A | 19920115 | IL 1987-82710 | 19870529 |
| PRIORITY APPLN. INFO.: | | | GB 1986-13183 | A 19860530 |
| | | | EP 1987-304776 | A 19870529 |

AB The title compound (I.isethionate), useful as an anticonvulsant (no data), was prepared by reaction of I with 2-hydroxyethanesulfonic acid (II) or by reaction of I salts with the anion of II. A 1.0 M solution of Na isethionate in H2O was passed through a column of IR 120 (H) ion exchange resin. I (preparation given) was added to the resulting II and the solution was filtered and evaporated Recrystn. from industrial methylated spirit gave 72% I.isethionate.

L10 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1985:542021 HCAPLUS
DOCUMENT NUMBER: 103:142021
TITLE: Triazine compounds having cardiovascular activity
INVENTOR(S): Allan, Geoffrey; Miller, Alastair Ainslie; Sawyer, David Alan
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 142306 | A2 | 19850522 | EP 1984-307374 | 19841026 |
| EP 142306 | A3 | 19861120 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| US 4649139 | A | 19870310 | US 1984-663682 | 19841022 |
| DK 8405121 | A | 19850428 | DK 1984-5121 | 19841026 |
| FI 8404212 | A | 19850428 | FI 1984-4212 | 19841026 |
| AU 8434758 | A | 19850509 | AU 1984-34758 | 19841026 |





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| AU 564667 | B2 | 19870820 | | | |
| JP 60109577 | A | 19850615 | JP 1984-225636 | | 19841026 |
| DD 224033 | A5 | 19850626 | DD 1984-268757 | | 19841026 |
| HU 36102 | A2 | 19850828 | HU 1984-4003 | | 19841026 |
| HU 191566 | B | 19870330 | | | |
| ES 537104 | A1 | 19860416 | ES 1984-537104 | | 19841026 |
| ZA 8408388 | A | 19860625 | ZA 1984-8388 | | 19841026 |
| SU 1371500 | A3 | 19880130 | SU 1984-3805251 | | 19841026 |
| IL 73332 | A | 19880630 | IL 1984-73332 | | 19841026 |
| PL 144899 | B1 | 19880730 | PL 1984-250213 | | 19841026 |
| CA 1261328 | A1 | 19890926 | CA 1984-466473 | | 19841026 |
| PRIORITY APPLN. INFO.: | | | GB 1983-28757 | A | 19831027 |
| OTHER SOURCE(S): | MARPAT 103:142021 | | | | |

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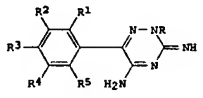

I

AB Tautomeric iminotriazinamines I [R = (un)substituted C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C3-10 cycloalkyl; R1-R5 = H, halogen, alkenyloxy, acyl, acyloxy, cyano, NO2, aryl, alkylthio, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, amino; R1R2, R2R3, R3R4, R4R5 = CH:CHCH:CH] were prepared Thus, 3,5-diamino-6-( 2,3-dichlorophenyl)-1,2, 4-triazine was alkylated with Me2CHI to give I-HI (R = Me2CH, R1 = R2 = Cl; R3-R5 = H) which was converted to the mesylate salt (II) (12% overall yield). II at 1 mg/kg i.v. to rats increased the amount of aconitine required to elicit ventricular arrhythmias by 490% compared with 84% for 1 mg/kg verapamil.



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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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http://www.cas.org/ONLINE/UG/regprops.html

=> s 84057-84-1/rn
L11 1 84057-84-1/RN

=> d scan

L11 1 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-
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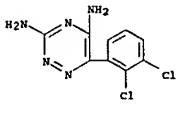
CI COM



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

ALL ANSWERS HAVE BEEN SCANNED

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 84.21 | 355.22 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -21.06 | -40.56 |

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STRUCTURE FILE UPDATES: 3 APR 2007 HIGHEST RN 929074-02-2
DICTIONARY FILE UPDATES: 3 APR 2007 HIGHEST RN 929074-02-2





=> file hcaplus

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
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| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | 0.00 | -40.56 |

FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007
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FILE COVERS 1907 - 4 Apr 2007 VOL 146 ISS 15
FILE LAST UPDATED: 3 Apr 2007 (20070403/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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FILE 'REGISTRY' ENTERED AT 16:55:37 ON 04 APR 2007
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L2 3 S L1 SSS SAM
L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
L4 25 S L3/P
E US20050238724/PN,PRN,AN
L5 0 S E3/RN
L6 1 S E3

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7 0 S L6

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
E LAMOTRIGINE+ALL/CT
S LAMOTRIGINE/CN

FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8 1 S LAMOTRIGINE/CN

FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9 1265 S L8
L10 27 S "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
L11 1 S 84057-84-1/RN

FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007

=> s l11
L12 1265 L11

=> s l10 or l12 and particle or granule
740429 PARTICLE
814603 PARTICLES
1234571 PARTICLE
(PARTICLE OR PARTICLES)
49055 GRANULE





86594 GRANULES
111146 GRANULE
(GRANULE OR GRANULES)
L13 111187 L10 OR L12 AND PARTICLE OR GRANULE

=> s l12 near particle
MISSING OPERATOR L12 NEAR
The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

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740429 PARTICLE
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1234571 PARTICLE
(PARTICLE OR PARTICLES)
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38387 CNS
L16 46 L12 AND CNS

=> d l16 1-46 ibib abs

L16 ANSWER 1 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:259533 HCAPLUS
DOCUMENT NUMBER: 146:302318
TITLE: 5-HT1B antagonist composition for treating CNS conditions
INVENTOR(S): Harrison, Wilma Marcia; Sobolov-Jaynes, Susan Beth; Foerster, Robert Sterling, Jr.; Van Beek, Jeroen Bernard
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 46pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007026219 | A2 | 20070308 | WO 2006-IB2364 | 20060821 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, | | | | |





GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
JP 2007063277 A 20070315 JP 2006-233101 20060830
PRIORITY APPLN. INFO.: US 2005-712954P P 20050831
AB The present invention relates to pharmaceutical compns. comprising 5-HT1B antagonists in combination with noradrenaline re-uptake inhibitor (NRI) or serotonin noradrenaline reuptake inhibitor (SNRI) and optionally a pharmaceutically acceptable carrier, and to their medicinal use in treating or preventing CNS conditions such as depression, anxiety, cognitions, ADHD, and comorbid indications.

L16 ANSWER 2 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:226913 HCAPLUS
DOCUMENT NUMBER: 146:280994
TITLE: Reducing myocardial damage and the incidence of arrhythmia arising from loss, reduction or interruption in coronary blood flow
INVENTOR(S): Weiss, Steven Michael
PATENT ASSIGNEE(S): Australia
SOURCE: PCT Int. Appl., 47pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007022568 | A1 | 20070301 | WO 2006-AU1207 | 20060824 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

PRIORITY APPLN. INFO.: AU 2005-904615 A 20050825
AB A method and composition is disclosed for reducing the extent of cardiac arrhythmias, both resulting from loss, decrease or interruption to the blood supply such as may happen during a heart attack or during cardiac surgery, in mammals. In particular, the present invention relates to a method of limiting or preventing cardiac cell damage and/or death, and limiting or preventing lethal or non-lethal cardiac arrhythmias, in a human, by administering to the cardiac cells a compound which selectively blocks or partially blocks persistent sodium currents and/or persistent sodium channels of cardiac cells. The composition involves any physiol. acceptable chemical or pharmaceutical composition comprising as its active ingredient a cardiac persistent sodium current and/or persistent sodium channel blocker.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:136851 HCAPLUS





TITLE: Recent advances in anti-epileptic drugs
AUTHOR(S): Khan, S. A.; Lamba, H. S.; Rathour, Arvind; Budhwaar, Vikas; Pahwa, Rakesh; Manjusha
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, 110 062, India
SOURCE: Asian Journal of Chemistry (2007), 19(2), 823-835
CODEN: AJCHEW; ISSN: 0970-7077
PUBLISHER: Asian Journal of Chemistry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Epilepsies are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread. Some newer anti-epileptic drugs have recently been developed. They have some advantages over the older drugs. These newer drugs may control seizures more effectively. They are effective in complex partial and secondary generalized seizures. These are felbamate, vigabatrin, gabapetin, clobazam, lamotrigine, oxcarbazepine, tiagabine, topiramate, fosphenytoin, and zonisamide.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:61845 HCAPLUS
DOCUMENT NUMBER: 146:135588
TITLE: Neuroprotective carbamate derivs. for treatment of neurodegenerative disorders
INVENTOR(S): Zhao, Boyu; Tywman, Roy E.
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V., Belg.
SOURCE: PCT Int. Appl., 83pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007008562 | A2 | 20070118 | WO 2006-US26291 | 20060707 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 2007021500 | A1 | 20070125 | US 2006-481601 | 20060706 |

PRIORITY APPLN. INFO.: US 2005-698403P P 20050712
OTHER SOURCE(S): MARPAT 146:135588
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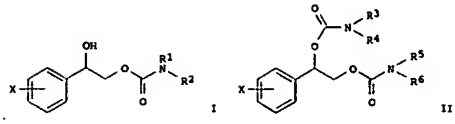

I II

AB This invention is directed to methods for providing neuroprotection comprising administering to a subject in need thereof a therapeutically effective amount of a compound selected from Formula (I) and Formula (II), where Ph is substituted at X with 1-5 halo atoms selected from F, C, B or I and R1-R6 = (un)substituted C1-C4 alkyl or pharmaceutical acceptable salts or esters thereof. Carbamate derivative decreased infarct volume following reperfusion in a rat model of transient cerebral ischemia arising from middle cerebral artery occlusion.

L16 ANSWER 5 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:61839 HCAPLUS
DOCUMENT NUMBER: 146:156257
TITLE: Carbamate compounds for treating epileptogenesis
INVENTOR(S): Twyman, Roy E.; Zhao, Boyu
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V, Belg.
SOURCE: PCT Int. Appl., 82pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007008551 | A2 | 20070118 | WO 2006-US26277 | 20060707 |
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| US 2007021501 | A1 | 20070125 | US 2006-481626 | 20060706 |
| PRIORITY APPLN. INFO.: | | | US 2005-698625P | P 20050712 |
| OTHER SOURCE(S): | | MARPAT 146:156257 | | |

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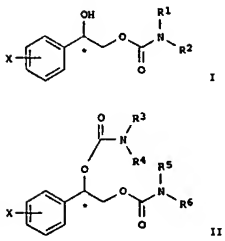

I II

AB The invention is directed to methods for preventing, treating, reversing, inhibiting, or arresting epileptogenesis in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound selected from the group consisting of Formula (I) and Formula (II),, where Ph is substituted at X with F, Cl, Br, or I; and R1-R6 = (un)substituted CrC4 alkyl or a pharmaceutically acceptable salt or ester thereof. A carbamate compound demonstrated anti-epileptogenic effects in rat model of spontaneous seizures.

L16 ANSWER 6 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1207236 HCAPLUS
DOCUMENT NUMBER: 145:495703
TITLE: Methods and compositions for the treatment of CNS-related conditions
INVENTOR(S): Went, Gregory T.; Fultz, Timothy J.
PATENT ASSIGNEE(S): Neuromolecular Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 58pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2006121560 | A2 | 20061116 | WO 2006-US13506 | 20060406 |
| WO 2006121560 | A3 | 20070315 | | |
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| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, | | | | |





KG, KZ, MD, RU, TJ, TM

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| US 2006142398 | A1 | 20060629 | US 2005-285905 | 20051122 |
| PRIORITY APPLN. INFO.: | | | US 2005-669290P | P 20050406 |
| | | | US 2005-285905 | A 20051122 |
| | | | US 2004-630885P | P 20041123 |
| | | | US 2004-635365P | P 20041210 |
| | | | US 2005-701857P | P 20050722 |

AB In general, the present invention provides methods and compns. for treating and preventing CNS-related conditions, such as neurodegenerative conditions (e.g., Alzheimer's disease and Parkinson's disease) and pain, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and a second agent such as acetylcholinesterase inhibitor (ACheI).

L16 ANSWER 7 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1173916 HCAPLUS
DOCUMENT NUMBER: 145:477933
TITLE: Methods and compositions for the treatment of CNS-related conditions
INVENTOR(S): Went, Gregory T.; Fultz, Timothy J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 29pp., Cont.-in-part of U.S. Ser. No. 285,905.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2006252788 | A1 | 20061109 | US 2006-399879 | 20060406 |
| US 2006142398 | A1 | 20060629 | US 2005-285905 | 20051122 |
| PRIORITY APPLN. INFO.: | | | US 2005-669290P | P 20050406 |
| | | | US 2005-285905 | A2 20051122 |
| | | | US 2004-630885P | P 20041123 |
| | | | US 2004-635365P | P 20041210 |
| | | | US 2005-701857P | P 20050722 |

AB The present invention provides novel methods and compns. for the treatment and prevention of CNS-related conditions. One of the CNS-related conditions treated by the methods and compns. of the invention is Alzheimer's disease.

L16 ANSWER 8 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:804735 HCAPLUS
DOCUMENT NUMBER: 146:243958
TITLE: Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings
AUTHOR(S): Clemens, Bela; Menes, Andrea; Piros, Palma; Bessenyei, Monika; Altmann, Anna; Jerney, Judit; Koller, Katalin; Rosdy, Beata; Rozsavolgyi, Margit; Steinecker, Katalin; Hollody, Katalin
CORPORATE SOURCE: Epilepsy Center, Department of Neurology, Kenezy Gyula Memorial Hospital, Debrecen, 4031, Hung.
SOURCE: Epilepsy Research (2006), 70(2-3), 190-199
CODEN: EPIRES; ISSN: 0920-1211
PUBLISHER: Elsevier Ltd.





DOCUMENT TYPE: Journal
LANGUAGE: English
AB Quant. EEG (QEEG) effects of therapeutic doses of carbamazepine (CBZ), oxcarbazepine (OXC), valproate (VA) and lamotrigine (LA) monotherapy were investigated in patients with beginning epilepsy. Baseline waking EEG (EEG1) was recorded in the untreated state, the second EEG (EEG2) was done after 8 wk of reaching the therapeutic dose. Left occipital data were used for anal. QEEG target parameters were absolute band-power (delta: AD, theta: AT, alpha: AA, beta: AB), and alpha mean frequency (AMF). Group effects (untreated vs. treated condition in the CBZ, VA, OXC, LA groups) were computed for each target parameter. One group with benign rolandic epilepsy remained untreated for clin. reasons and served to estimate the QEEG test-retest differences. In addition, the individual QEEG response to each drug was calculated as (EEG2 - EEG1). Results: statistically significant ($p < 0.05$) group differences indicated the QEEG domain systematically affected by the drugs. CBZ caused AT increase and AMF decrease. OXC caused AMF decrease. VA and LA did not decrease AMF (LA even increased it), but reduced broad-band power. Individual power and AMF changes showed considerable variability in each group. >0.5 Hz AMF decrease (that was reported to predict cognitive impairment in prior studies) occurred in 10/41 patients in the CBZ group but never in the OXC, VA, LA groups. The results may be utilized in planning further studies addressing the relationship between antiepileptic drugs and their CNS effects. In addition, the relationship of AED-related cognitive impairment and AMF changes was discussed.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:740619 HCAPLUS
DOCUMENT NUMBER: 145:159852
TITLE: Method for treating borderline personality disorder and self-injurious behavior with glutamate-modulating agents
INVENTOR(S): Feuerstein, Seth; Coric, Vladimir
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2006167068 | A1 | 20060727 | US 2006-339881 | 20060126 |
| PRIORITY APPLN. INFO.: | | | US 2005-647535P | P 20050126 |

AB Glutamate-modulating agents are useful for treating borderline personality disorder and self-injurious behavior. Methods for treating borderline personality and self-injurious behavior are provided which involve administering a glutamate-modulating agent to a patient. The invention also includes combination methods of treatment in which a glutamate-modulating agent is administered with one or more other CNS active agents. Packaged pharmaceutical compns. containing a glutamate-modulating agent and one or more other CNS agent are also provided, as are packaged pharmaceutical formulations containing a glutamate-modulating agent and instructions for using the glutamate-modulating agent for treating borderline personality disorder or self-mutilating behavior.

L16 ANSWER 10 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:493860 HCAPLUS
DOCUMENT NUMBER: 144:481072
TITLE: Methods and compositions for treating pain
INVENTOR(S): Robbins, Wendye
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 61 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2006111307 | A1 | 20060525 | US 2005-281771 | 20051116 |
| US 2006111308 | A1 | 20060525 | US 2005-281984 | 20051116 |
| WO 2006055672 | A2 | 20060526 | WO 2005-US41608 | 20051116 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| GB 2423928 | A | 20060913 | GB 2006-6028 | 20051116 |
| PRIORITY APPLN. INFO.: | | | US 2004-628646P | P 20041116 |
| | | | WO 2005-US41608 | W 20051116 |

AB Methods and compns. are described for the modulation of central nervous system and/or fetal effects of substances. Methods and compns. are described for the modulation of efflux transporter activity to increase the efflux of drugs and other compds. out of a physiol. compartment and into an external environment. In particular, the methods and compns. disclosed herein provide for the increase of efflux transporter activity at blood-brain, blood-CSF and placental-maternal barriers to increase the efflux of drugs and other compds. from physiol. compartments, including central nervous system and fetal compartments.

L16 ANSWER 11 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:383992 HCAPLUS
DOCUMENT NUMBER: 144:404414
TITLE: Carbamate compounds for use in treating neurodegenerative disorders
INVENTOR(S): Twyman, Roy E.; Zhao, Boyu
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V., Belg.
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|





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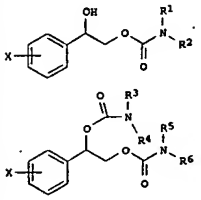
|---|---|---|---|---|
| WO 2006044472 | A1 | 20060427 | WO 2005-US36695 | 20051014 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| PRIORITY APPLN. INFO.: | | | US 2004-619402P | P 20041015 |
| | | | US 2005-698403P | P 20050712 |

OTHER SOURCE(S): MARPAT 144:404414
GI



I



II

AB The invention discloses methods for providing neuroprotection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound I or II [Ph is substituted at X with 1-5 halo atoms selected from F, Cl, Br, I; R1-R6 = H, (un)substituted C1-C4 alkyl], or a pharmaceutically acceptable salt or ester thereof.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 12 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:333530 HCAPLUS
DOCUMENT NUMBER: 144:324867
TITLE: Methods of treating epileptogenesis and epilepsy
INVENTOR(S): Choi, Yong Moon; Gordon, Robert; Novak, Gerald P.; Plata-Salaman, Carlos R.; Twyman, Roy E.; White, H. Steve; Zhao, Boyu
PATENT ASSIGNEE(S): Janssen Pharmaceutica, N.V., Belg.
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent





LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006033947 | A2 | 20060330 | WO 2005-US32861 | 20050915 |
| WO 2006033947 | A3 | 20060629 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| US 2006194873 | A1 | 20060831 | US 2005-227247 | 20050915 |
| PRIORITY APPLN. INFO.: | | | US 2004-610276P | P 20040916 |
| | | | US 2005-698625P | P 20050712 |
| | | | US 2005-707242P | P 20050811 |

OTHER SOURCE(S): MARPAT 144:324867
AB This invention is directed to methods for preventing, treating, reversing, inhibiting or arresting epilepsy and epileptogenesis in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound selected from the group consisting of Formula (I) and Formula (II), or a pharmaceutically acceptable salt or ester thereof,: Formula (I) Formula (II) wherein Ph is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and, R1, R2, R3, R4, R5 and R6 are independently selected from the group consisting of hydrogen and C1-C4 alkyl; wherein C1-C4 alkyl is optionally substituted with Ph (wherein Ph is optionally substituted with substituents independently selected from the group consisting of halogen, C1-C4 alkyl, C1-C4 alkoxy, amino, nitro and cyano).

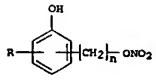
L16 ANSWER 13 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:149768 HCAPLUS
DOCUMENT NUMBER: 144:232798
TITLE: Preparation of nitroxyalkyl derivatives of phenol for treating inflammatory, cardiovascular and peripheral vascular diseases
INVENTOR(S): Ongini, Ennio; Impagnatiello, Francesco
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006015930 | A1 | 20060216 | WO 2005-EP53500 | 20050720 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, | | | | |





GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NO, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2004-599857P P 20040810
OTHER SOURCE(S): MARPAT 144:232798
GI



I

AB The title compds. I [n = 1-20; R = H, halo, a linear or branched (C1-C10)alkoxy, OH, CF3, NHR' (wherein R' = H or a linear or branched (C1-C10)alkyl); or a salt thereof], useful for treating inflammatory disease states or disorders, cardiovascular and/or peripheral vascular diseases, were prepared E.g., a benzenemethanol, 3-hydroxy-α-nitrate (II) was prepared from com. available 3-[(hydroxy)methyl]phenol using 2-step process. Effects of II on inflammatory markers were tested. For example, the compound II applied alone or in combination with ASA inhibited LPS/INFγ-induced nitrites accumulation with similar potency as that estimated for NCX 4016 (EC50 = 58 μM and 57 μM, resp. for compound II alone and in combination with ASA). The pharmaceutical compns. comprising the compound II alone or in combination with other therapeutic agents are disclosed.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 14 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:149494 HCAPLUS
DOCUMENT NUMBER: 144:205795
TITLE: Preventing pathological increases in the rate of nerve cell suicide in immature nervous systems
INVENTOR(S): Olney, John W.
PATENT ASSIGNEE(S): Olney, John, W., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006017524 | A2 | 20060216 | WO 2005-US27460 | 20050802 |
| WO 2006017524 | A3 | 20060831 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, | | | | |

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-598390P P 20040802

AB Methods and compds. are disclosed for reducing brain damage in fetuses, neonates, and young infants, caused by surgical anesthetics. During critical periods of synapse formation and network development in the brain, CNS neurons that do not appear to be keeping pace with certain synchronized development and connection processes are regarded as surplus, and are destroyed by a programmed cell suicide process called apoptosis. As a result, if surgical anesthetics block neuronal responses and activities that normally would indicate that a certain CNS neuron is indeed active and involved in a network and should be preserved, such anesthesia can induce apoptotic death, in the unresponsive anesthetized neurons. That process, which can cause permanent brain damage, can be minimized by manipulating certain signaling pathways that affect the balance between apoptosis-promoting proteins ( e.g., Bax and Bak) and apoptosis-blocking proteins ( e.g., Bcl-2 and Bcl-xL). Agents that have been tested and shown to reduce anesthesia-induced brain damage in neonatal animals include xenon (which promotes ERK MAPKinase activity), and muscarinic cholinergic agonists (which can promote ERK MAPKinase, PKA, PKC, and/or PI3K/AKT activity). Other candidate agents with similar activities include lithium, beta-1 adrenergic antagonists, and beta-2 adrenergic agonists. Such agents must intervene in the "upstream" part of the apoptosis cascade, before mitochondrial membranes become permeable and begin to release "cytochrome c" messenger mols.

L16 ANSWER 15 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:962027 HCAPLUS
DOCUMENT NUMBER: 143:235530
TITLE: Methods and compositions for the treatment of epilepsy, seizure disorders, and other CNS disorders
INVENTOR(S): Went, Gregory; Fultz, Timothy J.; Meyerson, Lawrence
PATENT ASSIGNEE(S): Neuromolecular, Inc., USA; Neuromolecular Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005079773 | A2 | 20050901 | WO 2005-US4819 | 20050214 |
| WO 2005079773 | A3 | 20051027 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,





NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| AU 2005215767 | A1 | 20050901 | AU 2005-215767 | 20050214 |
| CA 2556214 | A1 | 20050901 | CA 2005-2556214 | 20050214 |
| EP 1727538 | A2 | 20061206 | EP 2005-732251 | 20050214 |

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

| | | | | |
|---|---|---|---|---|
| CN 1929830 | A | 20070314 | CN 2005-80007919 | 20050214 |

PRIORITY APPLN. INFO.: US 2004-544839P P 20040213
US 2004-603903P P 20040824
US 2004-635786P P 20041213
WO 2005-US4819 W 20050214

AB The present invention relates to compns. comprising an NMDA receptor antagonists and an anti-epileptic drug for the treatment of CNS -related disorders. For example, tablets were formulated containing memantine 10, topiramate 30, dicalcium phosphate dihydrate 26.6, microcryst. cellulose 26.6, Na starch glycolate 1.2, Mg stearate 0.6, Eudragit RS30D 4.76, talc 3.3, and tri-Et citrate 0.95 mg per tablet.

L16 ANSWER 16 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:673292 HCAPLUS
DOCUMENT NUMBER: 143:172866
TITLE: Preparation of isothiazole dioxides as CXC- and CC-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Zheng, Junying; Biju, Purakkattle J.; Yu, Younong; Chao, Jianhua; Fine, Jay; Lundell, Daniel; Priestley, Tony; Reggiani, Angelo; Merritt, J. Robert; Baldwin, John J.; Lai, Gaifa; Wu, Minglang
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 427 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005068460 | A1 | 20050728 | WO 2004-US42720 | 20041220 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| CA 2550540 | A1 | 20050728 | CA 2004-2550540 | 20041220 |
| US 2006025453 | A1 | 20060202 | US 2004-17505 | 20041220 |
| EP 1697354 | A1 | 20060906 | EP 2004-814856 | 20041220 |





R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU

| | | | | |
|---|---|---|---|---|
| CN 1918156 | A | 20070221 | CN 2004-80041794 | 20041220 |

PRIORITY APPLN. INFO.: US 2003-531693P P 20031222
WO 2004-US42720 W 20041220

OTHER SOURCE(S): MARPAT 143:172866
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed are novel compds. I [D, E = N, CR50; provided that D and E are not the same (one is N and the other is CR50); R50 = H, CF3, CN, etc.; A = (hetero)aryl, (hetero)arylalkyl; B = (hetero)aryl] and the pharmaceutically acceptable salts and solvates thereof. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, pain (e.g., acute pain, acute and chronic inflammatory pain, and neuropathic pain) using a compound I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 68% yield from the isothiazoledioxide III and the amine IV.pTSA (preparation of reactants given). Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 17 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:638859 HCAPLUS
DOCUMENT NUMBER: 143:153384
TITLE: Preparation of diaminothiadiazoles as CXC- and CC-chemokine receptor ligands
INVENTOR(S): Biju, Purakkattle J.; Taveras, Arthur G.; Yu, Younong; Zheng, Junying; Chao, Jianhua; Aki, Cynthia J.; Fine, Jay; Lundell, Daniel; Priestley, Tony; Reggiani, Angelo; Merritt, J. Robert; Baldwin, John J.
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 593 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005066147 | A1 | 20050721 | WO 2004-US42060 | 20041216 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| CA 2550189 | A1 | 20050721 | CA 2004-2550189 | 20041216 |
| EP 1694659 | A1 | 20060830 | EP 2004-814266 | 20041216 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU

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|---|---|---|---|---|
| US 2006123864 | A1 | 20061005 | US 2004-13753 | 20041216 |
| CN 1918138 | A | 20070221 | CN 2004-80041695 | 20041216 |

PRIORITY APPLN. INFO.: US 2003-531311P P 20031219
US 2003-531713P P 20031222
WO 2004-US42060 W 20041216

OTHER SOURCE(S): MARPAT 143:153384
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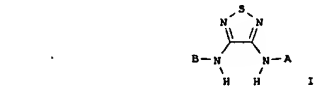
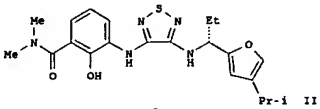
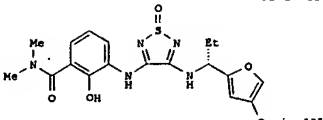


I



II



III

AB Disclosed are diaminothiadiazoles I [A = (hetero)aryl, (hetero)arylmethyl (substituted at CH2), etc.; B = (hetero)aryl] and the pharmaceutically acceptable salts and solvates thereof. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and ischemia reperfusion injury, acute pain, acute and chronic inflammatory and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 43% yield from its monooxide III (preparation given). Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7

are given.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 18 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:364521 HCAPLUS
DOCUMENT NUMBER: 143:126473
TITLE: Valproic acid, but not lamotrigine, suppresses seizure-induced c-fos and c-Jun mRNA expression
AUTHOR(S): Szot, Patricia; White, Sylvia S.; Shen, Danny D.; Anderson, Gail D.
CORPORATE SOURCE: Mental Illness Research Education and Clinical Center (MIRECC), VA Puget Sound Health Care System, Seattle, WA, 98108, USA
SOURCE: Molecular Brain Research (2005), 135(1-2), 285-289
CODEN: MBREE4; ISSN: 0169-328X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Seizure-induced activity was shown to increase the expression of immediate early genes (IEGs) c-fos and c-Jun in the CNS. Antiepileptic drugs (AEDs) can suppress the induction of a seizure, but it is unknown if AEDs affect the expression of seizure-induced IEGs. The authors found that valproic acid (VPA), but not lamotrigine (LTG), was capable of suppressing seizure-induced c-fos and c-Jun mRNA expression in rats despite a similar anticonvulsant effect. LTG in some regions of the CNS enhanced seizure-induced IEG expression. These studies indicate that the older AED (VPA), as compared to the newer AED (LTG), can suppress seizure-induced IEG expression. The consequence of this suppression of IEGs following a generalized seizure may be viewed either as a neuroprotective or detrimental effect upon the brain.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 19 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:288391 HCAPLUS
DOCUMENT NUMBER: 143:71550
TITLE: Adverse reactions of topiramate and lamotrigine in children
AUTHOR(S): Shechter, Tamar; Shorer, Zamir; Kramer, Uri; Lerman-Sagie, Tally; Ronen, Elisheva; Rotem, Rimona; Gorodischer, Rafael
CORPORATE SOURCE: Pharmacy Services, Soroka Medical Center, Be'er Sheva, Israel
SOURCE: Pharmacoepidemiology and Drug Safety (2005), 14(3), 187-192
CODEN: PDSAEA; ISSN: 1053-8569
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: To review the adverse drug reactions (ADRs) of Topiramate and Lamotrigine among children in Israel, and to compare the two drugs, based on their side effect profile and tolerability among this population. Methods: We performed a cross-sectional study. Four pediatric neurologists from three different tertiary medical centers in Israel documented all cases of children from birth to the age 18 years, treated with Topiramate and/or Lamotrigine in their resp. outpatient clinics and hospital wards. All present ADRs and their characteristics were recorded. Results: Reports on 45 and 65 children treated with Topiramate and





Lamotrigine resp., were received. Half of the children treated with Topiramate suffered from one or more ADRs, as opposed to one-third of the children treated with Lamotrigine (p = 0.03). Most reactions were considered mild to moderate. There were no deaths or hospitalizations, but the drug had to be discontinued in about 10% of the patients due to ADRs. Most Topiramate and Lamotrigine ADRs appeared early in the treatment and were more frequent when Topiramate was an add-on vs. a monotherapy drug. Most ADRs of both Topiramate and Lamotrigine were related to the central nervous system; while poor appetite, drowsiness, speech difficulties and weight loss were observed only with Topiramate, and rash and headaches only with Lamotrigine. Nervousness and seizure aggravation were more frequent ADRs of Topiramate whereas sleep disturbances were observed more in children treated with Lamotrigine. Conclusion: Results of this study indicate that Lamotrigine causes ADRs less frequently than Topiramate; however both medications are generally well tolerated. Topiramate and Lamotrigine differ in their central nervous system side effect profile.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 20 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:53346 HCAPLUS
DOCUMENT NUMBER: 142:290582
TITLE: Relationship between exposure and nonspecific binding of thirty-three central nervous system drugs in mice
AUTHOR(S): Maurer, Tristan S.; DeBartolo, Demetria B.; Tess, David A.; Scott, Dennis O.
CORPORATE SOURCE: Pharmacokinetics, Pharmacodynamics and Drug Metabolism, Pfizer Global Research and Development, Groton Laboratories, Groton, CT, USA
SOURCE: Drug Metabolism and Disposition (2005), 33(1), 175-181
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unbound fractions in mouse brain and plasma were determined for 31 structurally diverse central nervous system (CNS) drugs and two active metabolites. Three comparisons were made between in vitro binding and in vivo exposure data, namely: (1) mouse brain-to-plasma exposure vs. unbound plasma-to-unbound brain fraction ratio (fuplasma/fubrain), (2) cerebrospinal fluid-to-brain exposure vs. unbound brain fraction (fubrain), and (3) cerebrospinal fluid-to-plasma exposure vs. unbound plasma fraction (fuplasma). Unbound fraction data were within 3-fold of in vivo exposure ratios for the majority of the drugs examined (i.e., 22 of 33), indicating a predominately free equilibrium across the blood-brain and blood-CSF barriers. Some degree of distributional impairment at either the blood-CSF or the blood-brain barrier was indicated for 8 of the 11 remaining drugs (i.e., carbamazepine, midazolam, phenytoin, sulpiride, thiopental, risperidone, 9-hydroxyrisperidone, and zolpidem). In several cases, the indicated distributional impairment is consistent with other independent literature reports for these drugs. Through the use of this approach, it appears that most CNS-active agents freely equilibrate across the blood-brain and blood-CSF barriers such that unbound drug concns. in brain approx. those in the plasma. However, these results also support the intuitive concept that distributional impairment does not necessarily preclude CNS activity.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS





RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 21 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:53345 HCAPLUS
DOCUMENT NUMBER: 142:290581
TITLE: The impact of P-glycoprotein on the disposition of drugs targeted for indications of the central nervous system: Evaluation using the MDR1A/1B knockout mouse model
AUTHOR(S): Doran, Angela; Obach, R. Scott; Smith, Bill J.; Hosea, Natilie A.; Becker, Stacey; Callegari, Ernesto; Chen, Cuiping; Chen, Xi; Choo, Edna; Cianfrogna, Julie; Cox, Loretta M.; Gibbs, John P.; Gibbs, Megan A.; Hatch, Heather; Hop, Cornelis E. C. A.; Kasman, Ilana N.; LaPerle, Jennifer; Liu, JianHua; Liu, Xingrong; Logman, Michael; Maclin, Debra; Nedza, Frank M.; Nelson, Frederick; Olson, Emily; Rahematpura, Sandhya; Raunig, David; Rogers, Sabrinia; Schmidt, Kari; Spracklin, Douglas K.; Szewc, Mark; Troutman, Matthew; Tseng, Elaine; Tu, Meihua; Van Deusen, Jeffrey W.; Venkatakrishnan, Karthik; Walens, Gary; Wang, Ellen Q.; Wong, Diane; Yasgar, Adam S.; Zhang, Chenghong
CORPORATE SOURCE: Departments of Pharmacokinetics, Dynamics, and Drug Metabolism, Pfizer Global Research and Development, Groton Laboratories, Groton, CT, USA
SOURCE: Drug Metabolism and Disposition (2005), 33(1), 165-174
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thirty-two structurally diverse drugs used for the treatment of various conditions of the central nervous system (CNS), along with two active metabolites, and eight non-CNS drugs were measured in brain, plasma, and cerebrospinal fluid in the P-glycoprotein (P-gp) knockout mouse model after s.c. administration, and the data were compared with corresponding data obtained in wild-type mice. Total brain-to-plasma (B/P) ratios for the CNS agents ranged from 0.060 to 24. Of the 34 CNS-active agents, only 7 demonstrated B/P area under the plasma concentration curve ratios between P-gp knockout and wild-type mice that did not differ significantly from unity. Most of the remaining drugs demonstrated 1.1- to 2.6-fold greater B/P ratios in P-gp knockout mice vs. wild-type mice. Three, risperidone, its active metabolite 9-hydroxyrisperidone, and metoclopramide, showed marked differences in B/P ratios between knockout and wild-type mice (6.6- to 17-fold). Differences in B/P ratios and cerebrospinal fluid/plasma ratios between wild-type and knockout animals were correlated. Through the use of this model, it appears that most CNS-active agents demonstrate at least some P-gp-mediated transport that can affect brain concns. However, the impact for the majority of agents is probably minor. The example of risperidone illustrates that even good P-gp substrates can still be clin. useful CNS-active agents. However, for such agents, unbound plasma concns. may need to be greater than values projected using receptor affinity data to achieve adequate receptor occupancy for effect.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 22 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:927018 HCAPLUS





DOCUMENT NUMBER: 141:388733
TITLE: Compositions of a cyclooxygenase-2 selective inhibitor and a sodium ion channel blocker for the treatment of central nervous system damage
INVENTOR(S): Stephenson, Diane T.; Taylor, Duncan P.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004093811 | A2 | 20041104 | WO 2004-US12383 | 20040421 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004224940 | A1 | 20041111 | US 2004-829009 | 20040421 |
| PRIORITY APPLN. INFO.: | | | US 2003-464499P | P 20030422 |
| | | | US 2003-464830P | P 20030423 |

OTHER SOURCE(S): MARPAT 141:388733
AB The invention provides compns. and methods for the treatment of central nervous system damage in a subject. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic condition or a central nervous system traumatic injury comprising the administration to a subject of a sodium ion channel blocker in combination with a cyclooxygenase-2 selective inhibitor. Use for the treatment of stroke is specifically claimed.

L16 ANSWER 23 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:802560 HCAPLUS
DOCUMENT NUMBER: 141:301459
TITLE: Novel formulations and method of treatment
INVENTOR(S): Buxton, Ian Richard; Currie, Robin; Dela-Cruz, Myrna A.; Goodson, Gary Wayne; Karolak, Wlodzimierz; Maleki, Mehran; Iyer, Vijay Mohan; Gopal, Muppirala; Parr, Alan Frank; Sidhu, Jagdey Singh; Stagner, Robert Allen; Vijay-Kumar, Akunuri Venkata
PATENT ASSIGNEE(S): Can.
SOURCE: U.S. Pat. Appl. Publ., 29 pp., Cont.-in-part of U.S. Ser. No. 629,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

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|---|---|---|---|---|---|
| US 2004192690 | A1 | 20040930 | US 2003-726752 | | 20031204 |
| US 2005032799 | A1 | 20050210 | US 2003-629177 | | 20030729 |
| PRIORITY APPLN. INFO.: | | | GB 2002-17492 | A | 20020729 |
| | | | GB 2002-17493 | A | 20020729 |
| | | | GB 2003-13801 | A | 20030613 |
| | | | US 2003-629177 | A2 | 20030729 |

AB A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof and methods of treatment and uses thereof are disclosed.

L16 ANSWER 24 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:740119 HCAPLUS
DOCUMENT NUMBER: 141:254587
TITLE: Methods and compositions for the treatment of chronic pain using dehydroepiandrosterone (DHEA) and derivatives thereof, alone or in combination with another drug
INVENTOR(S): Lucas, John M.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004075832 | A2 | 20040910 | WO 2004-US4861 | 20040219 |
| WO 2004075832 | A3 | 20050324 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|---|
| US 2006178354 | A1 | 20060810 | US 2005-546882 | | 20050826 |
| PRIORITY APPLN. INFO.: | | | US 2003-450271P | P | 20030227 |
| | | | WO 2004-US4861 | W | 20040219 |

AB The invention relates to the treatment of chronic pain using DHEA or derivs. thereof either alone or in combination with at least one other drug. The invention also includes compns. comprising DHEA or a derivative thereof and a second drug.

L16 ANSWER 25 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:120727 HCAPLUS
DOCUMENT NUMBER: 140:169680
TITLE: Sustained release formulations comprising lamotrigine
INVENTOR(S): Buxton, Ian Richard; Currie, Robin; Dela-Cruz, Myrna A.; Goodson, Gary Wayne; Karolak, Wlodzimierz; Maleki, Mehran; Iyer, Vijay Mohan; Muppirala, Gopel; Parr, Alan Frank; Sidhu, Jagdev Singh; Stagner, Robert Allen; Vijay-kumar, Akunuri Venkata
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; et al.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent





LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004012741 | A1 | 20040212 | WO 2003-EP8368 | 20030728 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|---|
| CA 2493301 | A1 | 20040212 | CA 2003-2493301 | | 20030728 |
| AU 2003260336 | A1 | 20040223 | AU 2003-260336 | | 20030728 |
| EP 1524981 | A1 | 20050427 | EP 2003-766343 | | 20030728 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | | |
| BR 2003013148 | A | 20050712 | BR 2003-13148 | | 20030728 |
| CN 1681509 | A | 20051012 | CN 2003-822371 | | 20030728 |
| JP 2005538113 | T | 20051215 | JP 2004-525362 | | 20030728 |
| NO 2005000948 | A | 20050222 | NO 2005-948 | | 20050222 |
| PRIORITY APPLN. INFO.: | | | GB 2002-17492 | A | 20020729 |
| | | | GB 2002-17493 | A | 20020729 |
| | | | GB 2003-13801 | A | 20030613 |
| | | | WO 2003-EP8368 | W | 20030728 |

AB A sustained-release formulation, especially tablet, of lamotrigine or its derivative
for treatment of CNS disorder comprises (by weight) 2.5 to 80% lamotrigine or its derivative, 10 to 70% release retarding polymer, 0 to 70% diluent, 0 to 20% compression aid, and 0.1 to 2.5% lubricant. Substantially all the lamotrigine or a pharmaceutically acceptable derivative is released from the formulation in a period of 2 to 20 h after administration to a patient, producing an Area Under the Curve value of 80 to 125% and Cmax of about 30% less than that of an instant-release tablet containing the same amount of lamotrigine. For example, a tablet formulation (Diffcore device) was prepared comprising (i) a core containing lamotrigine 200 mg, a blend of hydroxypropyl Me celluloses K100LV 62.64 mg and E4M 45.36 mg, lactose monohydrate 90.4 mg, and magnesium stearate 1.6 mg, and (ii) an outer coat containing Eudragit L30 D-55 (30% weight/weight solution) 17.3 mg, Red
Iron Oxide 0.37 mg, tri-Et citrate 1.81 mg, glyceryl monostearate 0.494 mg, and Polysorbate 80 0.02 mg. The coating included orifices allowing the release of lamotrigine from the core.

L16 ANSWER 26 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:61937 HCAPLUS
DOCUMENT NUMBER: 141:342
TITLE: Brain access and anticonvulsant efficacy of carbamazepine, lamotrigine, and felbamate in ABCC2/MRP2-deficient TR- rats
AUTHOR(S): Potschka, Heidrun; Fedrowitz, Maren; Loescher, Wolfgang
CORPORATE SOURCE: Department of Pharmacology, Toxicology, and Pharmacy, School of Veterinary Medicine, Hannover, Germany





SOURCE: Epilepsia (2003), 44(12), 1479-1486
CODEN: EPILAK; ISSN: 0013-9580
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Different ATP (ATP)driven multidrug transporters have been described to be expressed in the luminal membrane of blood-brain barrier (BBB) endothelial cells. At this site, multidrug transporters have been suggested to restrict penetration of drugs into the brain. Increasing evidence suggests that overexpression of different multidrug transporters occurs in the region of the epileptic focus of pharmacoresistant epilepsy patients. Based on the assumption that antiepileptic drugs (AEDs) are substrates of these transporters, this overexpression may limit access of AEDs to epileptic neurons and may contribute to drug-refractoriness. In a recent study, overexpression of multidrug resistance protein 2 (ABCC2; MRP2) was reported in BBB endothelial cells of epileptic focal tissue from pharmacoresistant patients. With brain microdialysis, we recently demonstrated that the AED phenytoin is subject to transport by ABCC2 at the BBB, whereas phenobarbital does not seem to be a substrate of ABCC2. We investigated whether ABCC2 is functionally involved in transport of the AEDs carbamazepine (CBZ), lamotrigine (LTG), and felbamate (FBM) across the BBB. The distribution of these AEDs into the brain of ABCC2-deficient TR- rats was determined AED concns. in plasma and brain extracellular space of these mutant rats did not differ significantly from those of rats of the corresponding background strain. In the amygdalakindling model of epilepsy, the anticonvulsant efficacy of LTG and FBM was comparable in both groups of rats. In contrast, CBZ exhibited a higher anticonvulsant activity in kindled ABCC2-deficient rats as compared with nonmutant rats. In this present study, the microdialysis results gave no evidence that ABCC2 function modulates entry of CBZ, LTG, and FBM into the CNS of naive rats. However, ABCC2 deficiency was associated with an increased anticonvulsant response of CBZ in the kindling model. Future investigations are planned to identify the underlying mechanism for this difference, clarifying whether a pharmacokinetic difference is detectable only when brain access of CBZ is compared in kindled ABCC2-deficient rats and kindled nonmutant rats, which may have an increased expression of ABCC2 in response to seizures. The data substantiate that ABCC2-deficient TR- rats are a useful tool for defining the role of ABCC2 for transport of AEDs, and give evidence that the use of kindled TR- rats may provide important supplementary information.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 27 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:962301 HCAPLUS
DOCUMENT NUMBER: 141:1649
TITLE: Glutamate-dependent regulation of cholinergic phenotype in hypothalamic neurons
AUTHOR(S): Belousov, Andrei B.
CORPORATE SOURCE: Department of Cell and Molecular Biology, Tulane University, New Orleans, LA, 70118, USA
SOURCE: NeuroReport (2003), 14(18), 2445-2449
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamate NMDA receptor antagonists are used clin. However, they have serious side effects, some of which are presumably due to an increase in acetylcholine transmission. The authors' previous expts. revealed





acetylcholine-dependent excitation in rat hypothalamic cultures after a chronic glutamate receptor blockade. Dextromethorphan, amantadine, and eliprodil are NMDA receptor antagonists. Lamotrigine inhibits synaptic glutamate release. These drugs are used clin. Here, using calcium imaging and immunocytochem., the authors demonstrate that a chronic treatment with each of these drugs induced acetylcholine activity and choline acetyltransferase immunoreactivity in rat hypothalamic (but not cortical) cultures. These data support the possibility that some side effects of anti-glutamate drugs in vivo may be due to the increase in cholinergic properties in certain regions of the CNS.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 28 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:769633 HCAPLUS
DOCUMENT NUMBER: 140:263619
TITLE: Relationship between lamotrigine oral dose, serum level and its inhibitory effect on CNS: insights from transcranial magnetic stimulation
AUTHOR(S): Tergau, Frithjof; Wischer, Stephan; Somal, Hardyal S.; Nitsche, Michael A.; Mercer, A. Joe; Paulus, Walter; Steinhoff, Bernhard J.
CORPORATE SOURCE: Department of Clinical Neurophysiology, University of Gottingen, Gottingen, D-37075, Germany
SOURCE: Epilepsy Research (2003), 56(1), 67-77
CODEN: EPIRE8; ISSN: 0920-1211
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antiepileptic drug lamotrigine (LTG) is known to reduce cortical excitability evaluated by transcranial magnetic stimulation (TMS). We investigated the relationship between LTG oral dosages, serum levels and inhibitory effects on resting motor threshold (RMT), a parameter of motor system excitability assessed by TMS. In a randomized, placebo-controlled crossover study 16 male volunteers received 325 mg LTG as a single dose, as bi-hourly graded cumulative dose, or placebo. RMT and serum levels were measured before and after 2-8 h. With single dose, RMT elevation showed a poor but significant correlation to serum levels. With graded dose, serum levels as well as RMT increased dose-dependently with significant ($P<0.0001$) linear correlation. However, detailed comparison showed a high inter-individual variability in the relationship resembling a sigmoid correlation. Different mechanisms besides the sodium-channel blockage as the main mode of action of LTG are discussed to explain the diversity of individual dose-response relationships. Provided that the RMT elevation reflects the antiepileptic potential of LTG, TMS may be developed as a tool to monitor interindividual response of epilepsy patients to LTG treatment as well as to explore efficacy of other antiepileptic drugs with similar mode of action.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 29 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:376842 HCAPLUS
DOCUMENT NUMBER: 138:385297
TITLE: Methods for treating depression and other CNS disorders using enantiomerically enriched desmethyl- and didesmethyl- metabolites of citalopram
INVENTOR(S): Bush, Larry R.; Currie, Mark G.; Senanayake, Chris H.; Fang, Kevin Q.

PATENT ASSIGNEE(S): Sepracor, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003040121 | A1 | 20030515 | WO 2002-US35408 | 20021105 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2465186 | A1 | 20030515 | CA 2002-2465186 | 20021105 |
| AU 2002356903 | A2 | 20030519 | AU 2002-356903 | 20021105 |
| EP 1446396 | A1 | 20040818 | EP 2002-802848 | 20021105 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| BR 2002013949 | A | 20040831 | BR 2002-13949 | 20021105 |
| HU 2004001934 | A2 | 20050128 | HU 2004-1934 | 20021105 |
| JP 2005510518 | T | 20050421 | JP 2003-542167 | 20021105 |
| CN 1705654 | A | 20051207 | CN 2002-822084 | 20021105 |
| IN 2004KN00505 | A | 20060616 | IN 2004-KN505 | 20040419 |
| ZA 2004003409 | A | 20051026 | ZA 2004-3409 | 20040505 |
| US 2004266864 | A1 | 20041230 | US 2004-842055 | 20040507 |
| NO 2004002013 | A | 20040514 | NO 2004-2013 | 20040514 |

PRIORITY APPLN. INFO.: US 2001-337606P P 20011108
WO 2002-US35408 W 20021105

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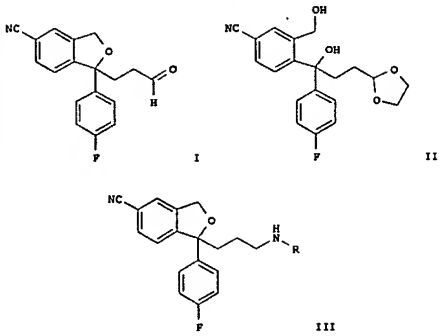


I II III

AB This invention relates to the preparation of I and II and derivs. of I and II in their racemic, enantiomerically enriched, or optically pure forms. This invention further relates to novel compns. of matter containing enantiomerically enriched (-)-desmethylcitalopram (-)-III (R = Me), (+)-didesmethylcitalopram (+)-III (R = Me), or (-)-didesmethylcitalopram (-)-III (R = H) or mixts. thereof in optimal ratios. Contrary to prior teachings, the enantiomerically enriched citalopram metabolites disclosed herein possess potent serotonin reuptake inhibitory activity, with minimal inhibitory effects on the reuptake of other known monoamines, e.g., norepinephrine (NE) or dopamine (DA). For example, stepwise reaction of 1-oxo-1,3-dihydroisobenzofuran-5-carbonitrile with 4-fluorophenylmagnesium bromide and the chiral Grignard reagent, which was prepared from 2-(2-bromoethyl)-[1,3]dioxolane and Mg powder, in THF gave II. Cyclization using mesyl chloride in CH2Cl2, followed by reduction provided the I. Reaction of the aldehyde with (-)-tert-butylsulfinamide in the presence of Ti(OEt)4 in EtOH afforded the sulfinamide, which was reduced to the amine III (R = H) with 10% HCl in MeOH. Protection of the amine with BOC anhydride in the presence of TEA in CH2Cl2 provided the enantiomerically enriched isomers, which were separated on a chiral column and subsequently deprotected with TFA to give (+)-III (R = H) and (-)-III (R = H). In biol. assays, (-)-III (R = H) and (+)-III (R = H) strongly inhibited serotonergic 5-HT receptor activity with Ki values of 5.8 nM and 90 nM, resp., with little effect on NE and DA transporter activity. By comparison, racemic citalopram inhibited serotonin reuptake with a Ki of 3.9 nM. The present invention also discloses methods for treating disorders, dysfunctions and diseases for which inhibition of serotonin reuptake is therapeutically beneficial. In particular, the present invention discloses a method for treating various forms of depression and other CNS disorders with pharmaceutical compns. described herein.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS





RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 30 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:319348 HCAPLUS
DOCUMENT NUMBER: 138:331688
TITLE: Methods of suppressing microglial activation and systemic inflammatory responses
INVENTOR(S): Laskowitz, Daniel T.; Matthew, William D.; McMillian, Michael
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 48 pp., Cont.-in-part of U.S. Ser. No. 957,909.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003077641 | A1 | 20030424 | US 2002-252120 | 20020923 |
| US 2002164789 | A1 | 20021107 | US 2001-957909 | 20010921 |

PRIORITY APPLN. INFO.: US 1998-77551P P 19980311
US 1999-260430 B2 19990301
US 2001-957909 A2 20010921

AB Methods of suppressing the activation of microglial cells in the Central Nervous System (CNS), methods of ameliorating or treating the neurol. effects of cerebral ischemia or cerebral inflammation, and methods of combating specific diseases that affect the CNS by administering a compound that binds to microglial receptors and prevents or reduces microglial activation are described. ApoE receptor binding peptides that may be used in the methods of the invention are also described, as are methods of using such peptides to treat peripheral inflammatory conditions such as sepsis. Also described are methods of screening compds. for the ability to suppress or reduce microglial activation. Injection of ApoE (133-149) in mice suppressed serum levels of TNFα and IL-6 following LPS administration.

L16 ANSWER 31 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:854041 HCAPLUS
DOCUMENT NUMBER: 139:111447
TITLE: Therapeutic Drug Monitoring of Lamotrigine in Patients Suffering from Resistant Partial Seizures
AUTHOR(S): Benetello, Pierpaola; Furlanut, Marco; Baraldo, Massimo; Tonon, Agnese; Furlanut, Mario
CORPORATE SOURCE: Department of Neurological Sciences, University of Padua, Padua, Italy
SOURCE: European Neurology (2002), 48(4), 200-203
CODEN: EUNEAP; ISSN: 0014-3022
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sixty patients, all potential candidates for ongoing lamotrigine (LTG) treatment as add-on therapy for resistant partial seizures and receiving carbamazepine (CBZ) and/or valproate (VPA) treatment, were submitted to therapeutic drug monitoring (TDM). The aim was to evaluate the possible relation between serum levels and the clin. effect of LTG, to verify whether CNS toxicity has to be considered the result of a pharmacokinetic or a pharmacodynamic interaction with CBZ, and to





investigate whether possible changes in the clin. response during long-term treatment are dependent on LTG serum level variations. Sixteen patients achieved complete control, 26 a ≥50% reduction in seizures, the remainder did not respond. Mean LTG serum concns. were higher in responders than in nonresponders, the difference being statistically insignificant. The best results were observed in VPA-cotreated patients with the highest LTG blood levels. CNS toxicity occurred after giving LTG to subjects who subsequently developed the highest LTG concns., whereas CNS toxicity seemed unrelated to CBZ and CBZ-epoxide serum concns. No decrease in LTG, CBZ and VPA serum levels was observed even in patients showing a reduction in the response during long-term treatment.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 32 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:797249 HCAPLUS
DOCUMENT NUMBER: 139:29927
TITLE: Anticonvulsants in central pain
AUTHOR(S): Finnerup, Nanna B.; Gottrup, Hanne; Jensen, Troels S.
CORPORATE SOURCE: Department of Neurology and Danish Pain Research Centre, Aarhus University Hospital, Aarhus, 8000, Den.
SOURCE: Expert Opinion on Pharmacotherapy (2002), 3(10), 1411-1420
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Treatment of central neuropathic pain (CP) following lesions of the CNS is a great challenge to the clinician. Preclin. and clin. studies indicate that neuronal hyperexcitability in damaged areas of the central nervous system plays a major role in the development of CP. Anticonvulsants are thought to act by increasing γ-aminobutyric acid-mediated inhibition, decreasing abnormal neuronal hyperexcitability by modulating sodium and calcium channels or by inhibiting excitatory amino acid actions. The resulting inhibition of excess neuronal activity is thought to be the basis for the use of anticonvulsants in epilepsy as well as neuropathic pain. Both first-generation anticonvulsant drugs (e.g., phenytoin, benzodiazepines, valproate and carbamazepine) and second-generation anticonvulsant drugs (e.g., lamotrigine, gabapentin and topiramate) are used in CP conditions. However, few randomized controlled trials on the treatment of this condition have been published. Present suggestions for anticonvulsant treatment of CP are lamotrigine as the first choice, followed by gabapentin or carbamazepine/oxcarbazepine. These compds. are considered as effective as the antidepressant amitriptyline.

REFERENCE COUNT: 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 33 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:672895 HCAPLUS
DOCUMENT NUMBER: 138:297430
TITLE: Lamotrigine derivatives and riluzole inhibit INa,P in cortical neurons
AUTHOR(S): Spadoni, Francesca; Hainsworth, Atticus Henry; Mercuri, Nicola Biagio; Caputi, Luigi; Martella, Giuseppina; Lavaroni, Franco; Bernardi, Giorgio; Stefani, Alessandro
CORPORATE SOURCE: IRCCS Fondazione Santa Lucia, Rome, Italy

SOURCE: NeuroReport (2002), 13(9), 1167-1170
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The persistent, slowly inactivating fraction of the sodium current (INa,P) is involved in key functions in the CNS such as dendritic integration of synaptic inputs and cellular excitability. We have studied whether established anti-epileptic drugs and neuroprotective agents target the persistent sodium current. Two lamotrigine derivs. (sipatrigine and 202W92) and riluzole inhibited the persistent sodium current at low, therapeutic concns. In contrast, lamotrigine and the classical antiepileptic agents phenytoin and valproic acid blocked the fast-inactivating sodium channel but failed to affect the persistent fraction. The ability to influence either mode of channel activity may represent a defining feature of each drug subclass, changing profoundly their clin. indications. Given the damaging role of a sustained influx of sodium in both pharmaco-resistant seizures or excitotoxic insults, we suggest the utilization of drugs that suppress the persistent conductance.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 34 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:488246 HCAPLUS
DOCUMENT NUMBER: 137:57576
TITLE: Methods and compositions using ion-dependent cotransporter modulators for treating conditions of the central and peripheral nervous systems using non-synaptic mechanisms
INVENTOR(S): Hochman, Daryl W.
PATENT ASSIGNEE(S): Cytoscan Sciences L.L.C., USA
SOURCE: U.S. Pat. Appl. Publ., 29 pp., Cont.-in-part of U.S. Ser. No. 470,637.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2002082252 | A1 | 20020627 | US 2002-56528 | | 20020123 |
| US 6495601 | B1 | 20021217 | US 1999-470637 | | 19991222 |
| US 2005267103 | A1 | 20051201 | US 2005-101000 | | 20050407 |
| US 2006025387 | A1 | 20060202 | US 2005-130945 | | 20050517 |
| US 2006089350 | A1 | 20060427 | US 2005-251724 | | 20051017 |
| US 2006035914 | A1 | 20060216 | US 2005-259532 | | 20051025 |
| PRIORITY APPLN. INFO.: | | | US 1998-113620P | P | 19981223 |
| | | | US 1999-470637 | A2 | 19991222 |
| | | | US 2001-263830P | P | 20010123 |
| | | | US 2002-56528 | A2 | 20020123 |
| | | | US 2005-101000 | A2 | 20050407 |
| | | | US 2005-130945 | A2 | 20050517 |

AB The invention discloses methods and compns. for treating selected conditions of the central and peripheral nervous systems employing non-synaptic mechanisms. More specifically, one aspect of the invention provides methods and materials for treating seizure and seizure disorders, epilepsy, status epilepticus, migraine, spreading depression, intracranial hypertension; for treating the pathophysiol. effects of head trauma,





stroke, ischemia and hypoxia; for treating or protecting from the pathophysiol. effects of neurotoxic agents such as ethanol; and for treating neurophsyciatric disorders and central nervous system edema by administering agents that modulate ionic concns. and/or ionic gradients in the brain, particularly ion-dependent or cation-chloride cotransporter antagonists. Electrolyte cotransport antagonists and combinations of such compns. with other agents for treating various conditions are disclosed. The invention also discloses methods and compns. for treating pain by administering ion-dependent cotransporter antagonists. Methods and compns. for enhancing cortical function, e.g. in centers of cognition, learning, and memory, by administering ion-dependent cotransporter agonists are disclosed.

L16 ANSWER 35 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:375796 HCAPLUS
DOCUMENT NUMBER: 137:5563
TITLE: Diet enriched with omega-3 fatty acids alleviates convulsion symptoms in epilepsy patients
AUTHOR(S): Schlanger, Simon; Shinitzky, Meir; Yam, Daniel
CORPORATE SOURCE: The Kalanit Institute for the Retarded Child, Rishon LeZion, Israel
SOURCE: Epilepsia (2002), 43(1), 103-104
CODEN: EPILAK; ISSN: 0013-9580
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We examined whether a dietary supplement containing omega-3 polyunsatd. fatty acids (n-3 PUFAs) can alleviate and/or reduce the frequency of epileptic seizures in patients with central nervous system (CNS) diseases treated with anticonvulsive drugs (ACDs). A special spread containing 65% n-3 PUFAs was added to the daily diet. The patients consumed 5 g of this spread at every breakfast for 6 mo. Five patients completed the study. In all of them, a marked reduction in both frequency and strength of the epileptic seizures was recorded. Incorporation of the dietary supplement containing n-3 PUFAs may be beneficial in suppression of some cases of epileptic seizures.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 36 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:195041 HCAPLUS
DOCUMENT NUMBER: 137:91443
TITLE: GABA and glutamate in migraine
AUTHOR(S): D'Andrea, Giovanni; Granella, Franco; Cataldini, Morena; Verdelli, Flavio; Balbi, Tiziana
CORPORATE SOURCE: Headache and Related Disorders Center, Pathology Unit, Este-Monselice Hospital, Este-Monselice, Italy
SOURCE: Journal of Headache and Pain (2001), 2(Suppl. 1), S57-S60
CODEN: JHPOAT; ISSN: 1129-2369
PUBLISHER: Springer-Verlag Italia Srl
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. GABA and glutamic acid are the main inhibitory and excitatory neurotransmitters of central nervous system. Among other functions they modulate the pain threshold in the CNS. For this reason it has been hypothesized that anomalies of GABA and glutamate turn-over may play a role in migraine pathogenesis. In this review are discussed the evidences in favor of this hypothesis. A derangement of GABA may be an





important factor in the occurrence of migraine attacks and their recurrence, whereas high level of glutamic acid may represent a biochem. marker of the neuronal hyperexcitability that may be the underlying cause of the aura. The pharmacol. modulation of metabolism of both neurotransmitters is a promising approach to improve migraine therapy. In particular the studies presented here suggest that gabaergic drugs may be useful in migraine without aura, antiglutamatergic drugs are indicated to treat migraine with aura.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 37 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:10280 HCAPLUS
DOCUMENT NUMBER: 136:64150
TITLE: GABA-ergic agonists for the treatment of age-related brain cortical dysfunction
INVENTOR(S): Leventhal, Audie G.
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002000221 | A1 | 20020103 | WO 2001-US19719 | 20010620 |
| W: AB, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2413405 | A1 | 20020103 | CA 2001-2413405 | 20010620 |
| AU 2001068609 | A5 | 20020108 | AU 2001-68609 | 20010620 |
| EP 1303280 | A1 | 20030423 | EP 2001-946582 | 20010620 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2004023952 | A1 | 20040205 | US 2002-311821 | 20021217 |
| AU 2006203432 | A1 | 20060831 | AU 2006-203432 | 20060809 |
| PRIORITY APPLN. INFO.: | | | US 2000-213388P | P 20000623 |
| | | | US 2001-277427P | P 20010320 |
| | | | WO 2001-US19719 | W 20010620 |

AB Methods are disclosed for the improvement of age-related decreases in cortical function by increasing the activity of inhibitory pathways, such as GABA-ergic pathways, in the central nervous system. In particular examples, subjects with age-related decreases in cortical function are treated by administration of therapeutically effective amts. of a GABA-ergic agonist. The disclosed methods also enable screening for drugs that inhibit an age-related decline in cortical function, for example by exposing a subject to a test agent, and measuring an increase in GABA-ergic cortical inhibitory activity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT





L16 ANSWER 38 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:904923 HCAPLUS
DOCUMENT NUMBER: 136:181219
TITLE: Effect of lamotrigine on the Ca2+-sensing cation current in cultured hippocampal neurons
AUTHOR(S): Xiong, Zhi-Gang; Chu, Xiang-Ping; MacDonald, J. F.
CORPORATE SOURCE: Robert S. Dow Neurobiology Laboratories, Legacy Clinical Research and Technology Center, Portland, OR, 97232, USA
SOURCE: Journal of Neurophysiology (2001), 86(5), 2520-2526
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

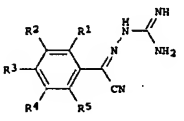
AB Concns. of extracellular calcium ([Ca2+]e) in the CNS decrease substantially during seizure activity. The authors have demonstrated previously that decreases in [Ca2+]e activate a novel calcium-sensing nonselective cation (csNSC) channel in hippocampal neurons. Activation of csNSC channels is responsible for a sustained membrane depolarization and increased neuronal excitability. This study has suggested that the csNSC channel is likely involved in generating and maintaining seizure activities. In the present study, the effects of anti-epileptic agent lamotrigine (LTG) on csNSC channels were studied in cultured mouse hippocampal neurons using patch-clamp techniques. At a holding potential of -60 mV, a slow inward current through csNSC channels was activated by a step reduction of [Ca2+]e from 1.5 to 0.2 mM. LTG decreased the amplitude of csNSC currents dose dependently with an IC50 of 171 ± 25.8 (SE) μM. The effect of LTG was independent of membrane potential. In the presence of 300 μM LTG, the amplitude of csNSC current was decreased by 31 ± 3% at -60 mV and 29 ± 2.9% at +40 mV ($P > 0.05$). LTG depressed csNSC current without affecting the potency of $Ca2+$ block of the current (IC50 for $Ca2+$ block of csNSC currents in the absence of LTG: 145 ± 18 μM; in the presence of 300 μM LTG: 136 ± 10 μM. n = 5, $P > 0.05$). In current-clamp recordings, activation of csNSC channel by reducing the [Ca2+]e caused a sustained membrane depolarization and an increase in the frequency of spontaneous firing of action potentials. LTG (300 μM) significantly inhibited csNSC channel-mediated membrane depolarization and the excitation of neurons. Fura-2 ratiometric $Ca2+$ imaging experiment showed that LTG also inhibited the increase in intracellular Ca2+ concentration induced by csNSC channel activation. The effect of LTG on csNSC channels may partially contribute to its broad spectrum of anti-epileptic actions.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 39 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:631908 HCAPLUS
DOCUMENT NUMBER: 135:195578
TITLE: Process for preparing substituted benzoyl cyanide amidinohydrazones as intermediates for synthesis of 3,5-diamino-6-phenyl-1,2,4-triazines
INVENTOR(S): Nadaka, Vladimir; Lexner, Jael; Kaspi, Joseph
PATENT ASSIGNEE(S): Chemagis Ltd., Israel
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1127873 | A2 | 20010829 | EP 2001-103660 | 20010223 |
| EP 1127873 | A3 | 20030507 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| IL 134730 | A | 20031031 | IL 2000-134730 | 20000225 |
| CA 2337280 | A1 | 20010825 | CA 2001-2337280 | 20010215 |
| HU 200100740 | A2 | 20011128 | HU 2001-740 | 20010215 |
| US 2001025118 | A1 | 20010927 | US 2001-789634 | 20010222 |
| US 6329521 | B2 | 20011211 | | |

PRIORITY APPLN. INFO.: IL 2000-134730 A 20000225
OTHER SOURCE(S): CASREACT 135:195578; MARPAT 135:195578
GI



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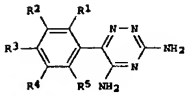
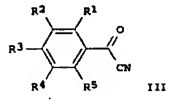


II



III

AB The title compds. [I; R1-R5 = H, halo, alkyl, etc.], useful as intermediates for synthesis of 1,2,4-triazines II (active in the treatment of CNS disorders), were prepared by reacting the benzoyl cyanides III with aminoguanidine bicarbonate in a mixture of a water-soluble solvent and polyphosphoric acid. Thus, reacting 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate in the presence of polyphosphoric acid in MeCN afforded 2,3-dichlorobenzoyl cyanide amidinohydrazone which was then heated under reflux in PrOH to give 2,3-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

L16 ANSWER 40 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:237425 HCAPLUS
DOCUMENT NUMBER: 130:291518
TITLE: Analysis of CSF amino acids in young patients with generalized refractory epilepsy during an add-on study with lamotrigine
AUTHOR(S): Eriksson, Ann-Sofie; O'Connor, William T.
CORPORATE SOURCE: Department of Pediatrics, Karolinska Hospital,





Stockholm, Swed.
SOURCE: Epilepsy Research (1999), 34(1), 75-83
CODEN: EPIRES; ISSN: 0920-1211
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of add-on administration of lamotrigine (1-12 mg/kg per day, 2-12 mo) on the levels of neurotransmission related amino acids including γ-aminobutyric acid (GABA), glutamate, aspartate, glycine and antiepileptic drugs (AEDs) in lumbar cerebrospinal fluid (CSF) was studied in 22 children and young adults with generalized therapy resistant epilepsy. Two lumbar punctures were performed, one prior to, and one following a mean of 5 mo (2-12 mo) of lamotrigine treatment. Lamotrigine decreased seizure incidence and severity in 12 of the 22 patients without influencing CSF GABA, glutamate, aspartate or glycine levels. Lamotrigine did not alter the concns. of AEDs in CSF or plasma. However, CSF GABA levels were 86% higher in those patients also treated with γ-vinyl-GABA (vigabatrin, GVG) compared with patients treated with other combinations and this was not altered by co-medication with lamotrigine. The proposed mechanism of action of lamotrigine, namely that it may inhibit glutamate release in the CNS, is not reflected by changes in CSF glutamate levels. The present findings indicate that CSF GABA, glutamate, aspartate and glycine levels may not be useful as in vivo neurochem. markers in young patients responding to the therapeutic dose of lamotrigine used in this study.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 41 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:567031 HCAPLUS
DOCUMENT NUMBER: 129:270545
TITLE: Mechanisms of deafferentation-induced plasticity in human motor cortex
AUTHOR(S): Ziemann, Ulf; Hallett, Mark; Cohen, Leonardo G.
CORPORATE SOURCE: Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892-1428, USA
SOURCE: Journal of Neuroscience (1998), 18(17), 7000-7007
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Deafferentation induces rapid plastic changes in the cerebral cortex, probably via unmasking of pre-existent connections. Several mechanisms may contribute, such as changes in neuronal membrane excitability, removal of local inhibition, or various forms of short- or long-term synaptic plasticity. To understand further the mechanisms involved in cortical plasticity, we tested the effects of CNS-active drugs in a plasticity model, in which forearm ischemic nerve block (INB) was combined with low-frequency repetitive transcranial magnetic stimulation (rTMS) of the deafferented human motor cortex. RTMS was used to upregulate the plastic changes caused by INB. We studied six healthy subjects. In two control sessions without drug application, INB plus rTMS increased the motor-evoked potential (MEP) size and decreased intracortical inhibition (ICI) measured with single- and paired-pulse TMS in the biceps brachii muscle proximal to INB. A single oral dose of the benzodiazepine lorazepam (2 mg) or the voltage-gated Na+ and Ca2+ channel blocker lamotrigine (300 mg) abolished these changes. The NMDA receptor blocker dextromethorphan (150 mg) suppressed the reduction in ICI but not the increase





in MEP size. With sleep deprivation, used to eliminate sedation as a major factor of these drug effects, INB plus rTMS induced changes similar to that seen in the control sessions. The findings suggest that (1) the INB plus rTMS-induced increase in MEP size involves rapid removal of GABA-related cortical inhibition and short-term changes in synaptic efficacy dependent on Na+ or Ca2+ channels and that (2) the long-lasting (>60 min) reduction in ICI is related to long-term potentiation-like mechanisms given its duration and the involvement of NMDA receptor activation.
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 42 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:105002 HCAPLUS
DOCUMENT NUMBER: 128:213312
TITLE: Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction?
AUTHOR(S): Besag, F. M. C.; Berry, D. J.; Pool, F.; Newbery, J. E.; Subel, B.
CORPORATE SOURCE: St Piers Lingfield, Surrey, RH7 6PW, UK
SOURCE: Epilepsia (1998), 39(2), 183-187
CODEN: EPILAK; ISSN: 0013-9580
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to determine whether the toxicity that occurs in some patients when lamotrigine (LTG) is added to carbamazepine (CBZ) is the result of either a pharmacokinetic or a pharmacodynamic interaction, escalating LTG doses were added to ongoing CBZ treatment in 47 patients. All patients had blood samples collected for drug concentration measurement, including the epoxide metabolite of CBZ, before starting LTG treatment and after stabilizing at each dose escalation. Patients also were examined for signs of toxicity. After LTG was introduced, nine patients demonstrated clin. signs of CNS toxicity, mainly diplopia and dizziness. There was no significant ($p = 0.05$) change in the serum concns. of either CBZ or its epoxide metabolite when LTG was added either to the group as a whole or to the nine patients who experienced adverse CNS effects. LTG serum concns. also were below the level at which the common signs of LTG toxicity, such as nausea, vomiting, or unsteadiness, are more likely to occur. In seven of the nine patients who exhibited CNS toxicity, CBZ serum concns. were >8 mg/L on LTG introduction. Toxicity is more likely to occur when LTG is added to CBZ if the initial CBZ level is high, typically >8 mg/L. This appears to be the result of a pharmacodynamic interaction. A reduction of CBZ dose usually resolves the toxicity, allowing the LTG dose to be escalated to maximal effect. It is not usually necessary to stop either drug.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 43 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:638497 HCAPLUS
DOCUMENT NUMBER: 125:315860
TITLE: Lamotrigine monotherapy: An overview
AUTHOR(S): Brodie, M. J.
CORPORATE SOURCE: WESTERN INFIRMARY, UNIVERSITY DEPARTMENT MEDICINE AND THERAPEUTICS, Glasgow, UK
SOURCE: International Congress and Symposium Series - Royal Society of Medicine (1996), 214(Lamotrigine--A





Brighter Future), 43-49
CODEN: RMISDU; ISSN: 0142-2367
PUBLISHER: Royal Society of Medicine Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with .apprx.5 refs. In a pooled population of 784 patients with newly-diagnosed epilepsy participating in comparative monotherapy trials, 443 were randomized to lamotrigine, 246 to carbamazepine and 95 to phenytoin. Overall, fewer patients were withdrawn due to adverse events on lamotrigine than with the older drugs (lamotrigine 9.5%, carbamazepine 19.1%, phenytoin 18.9%). Central nervous system (CNS) problems resulting in withdrawal, in particular, were infrequent with lamotrigine (lamotrigine 2.5%, carbamazepine 7.7%, phenytoin 7.4%). Withdrawal due to rash occurred in 6.1% of patients on lamotrigine, 8.9% on carbamazepine and 5.3% on phenytoin. The rash rate leading to withdrawal with lamotrigine appeared to relate to the initiation dose (100 mg, 11.8%; 50 mg, 9.2%; 25 mg, 2.2%). It is sometimes appropriate to substitute lamotrigine monotherapy for other antiepileptic drug treatments. Schedules for substituting lamotrigine in patients established on phenytoin, carbamazepine or sodium valproate are outlined. In the comparative monotherapy trials, the most popular lamotrigine doses were 150-200 mg daily. In studies in which concomitant antiepileptic drugs (AEDs) were withdrawn to achieve lamotrigine monotherapy, some patients took as much as 700 mg lamotrigine daily. Clin. experience to date does not suggest the existence of a relationship between the plasma lamotrigine concentration and its efficacy or toxicity. Data and case reports from a prospective study in Glasgow relating lamotrigine dosage and concentration to seizure control and the emergence of side effects are presented.

L16 ANSWER 44 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:94551 HCAPLUS
DOCUMENT NUMBER: 124:194132
TITLE: The effects of anticonvulsants on 4-aminopyridine-induced bursting: in vitro studies on rat peripheral nerve and dorsal roots
AUTHOR(S): Lees, G.
CORPORATE SOURCE: Dep. Academic Anaesthetics, Imperial College Medicine, London, W2 1NY, UK
SOURCE: British Journal of Pharmacology (1996), 117(3), 573-9
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aminopyridines have been used as beneficial symptomatic treatments in a variety of neurol. conditions including multiple sclerosis but have been associated with considerable toxicity in the form of abdominal pain, paraesthesias and (rarely) convulsions. Extracellular and intracellular recording was used to characterize action potentials in rat sciatic nerves and dorsal roots and the effects of 4-aminopyridine (4-AP). In sciatic nerve trunks, 1 mM 4-AP produced pronounced after potentials at room temperature secondary to regenerative firing in affected axons (5-10 spikes per stimulus). At physiol. temps., after potentials (2-3 spikes) were greatly attenuated in peripheral axons. 4-AP evoked more pronounced and prolonged after discharges in isolated dorsal roots at 37°C (3-5.5 mV and 80-100 ms succeeded by a smaller inhibitory/depolarizing voltage shift) which were used to assess the effects of anticonvulsants. Phenytoin, carbamazepine and lamotrigine dose-dependently reduced the area of 4-AP-induced after potentials at 100 and 320 μM but the amplitude of

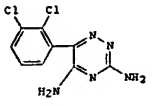
compound action potentials (evoked at 0.5 Hz) was depressed in parallel. The tonic block of sensory action potentials by all three drugs (at 320 μM) was enhanced by high frequency stimulation (5-500 Hz). The lack of selectivity of these frequency-dependent Na+ channel blockers for burst firing, compared to low-frequency spikes, is discussed in contrast to their effects on 4-AP-induced seizures and paroxysmal activity in CNS tissue (which is associated with large and sustained depolarizing plateau potentials). In conclusion, these in vitro results confirm the marked sensitivity of sensory axons to 4-AP (the presumptive basis for paraesthesias). Burst firing was not preferentially impaired at relatively high concns. suggesting that anticonvulsants will not overcome the toxic peripheral actions of 4-AP in neurol. patients.

L16 ANSWER 45 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:531450 HCAPLUS
DOCUMENT NUMBER: 119:131450
TITLE: Studies on the mechanism of action of the novel anticonvulsant lamotrigine (Lamictal) using primary neuroglial cultures from rat cortex
AUTHOR(S): Lees, George; Leach, Michael J.
CORPORATE SOURCE: Dep. Pharmacol., Wellcome Res. Lab., Beckenham/Kent, BR3 3BS, UK
SOURCE: Brain Research (1993), 612(1-2), 190-9
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Whole cell and perforated patch clamp expts. were conducted on cultured cortical rat neurons (7-21 days in vitro) in order to determine the effects of the anticonvulsant and glutamate release inhibitor lamotrigine (10-100 μM), on CNS receptors and ion channels. The compound inhibited, indiscriminately, both excitatory and inhibitory synaptic events which occurred spontaneously in cultured neural circuits. The drug did not mimic diazepam as a pos. modulator of GABAA currents. In the presence of tetrodotoxin, voltage-gated potassium currents and composite currents evoked by L-glutamate were not significantly modulated even at the highest dose. Unitary, fast, presumptive-sodium spikes, evoked at low frequencies, were not blocked significantly by lamotrigine. In contrast, burst firing induced by pulsed application of L-glutamate or potassium ions was markedly depressed at 10 μM. Presumptive calcium currents were inhibited by lamotrigine at 100 μM. It is proposed that the drug inhibits epileptiform burst firing preferentially by state/activity dependent interactions with voltage and gated cation channels. Potential mechanisms for inhibition of glutamate release are discussed.

L16 ANSWER 46 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:102360 HCAPLUS
DOCUMENT NUMBER: 104:102360
TITLE: Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam
AUTHOR(S): Cohen, A. F.; Ashby, L.; Crowley, D.; Land, G.; Peck, A. W.; Miller, A. A.
CORPORATE SOURCE: Wellcome Res. Lab., Beckenham/Kent, UK
SOURCE: British Journal of Clinical Pharmacology (1985), 20(6), 619-29
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English
GI







I

AB Healthy male volunteers received phenytoin [57-41-0] 0.5 and 1 g, lamotrigine (I) [84057-84-1] (a new anticonvulsant) 120 and 240 mg, diazepam [439-14-5] 10 mg and placebo orally in a double-blind, cross-over, randomized trail. Maximum drug concns. at 4 h, measured in plasma were 11.5 μg/mL for phenytoin and 2.7 μg/mL for lamotrigine. These levels were in the therapeutic range for phenytoin and the putative therapeutic range for lamotrigine. Side effects after diazepam (mainly sedation) and phenytoin (mainly unsteadiness) differed markedly from lamotrigine which produced no important side effects. Subjective effects as measured by visual analog scales were caused by phenytoin and diazepam but not by lamotrigine. Diazepam impaired eye movements, adaptive tracking and body sway. Phenytoin impaired adaptive tracking, increased body sway and impaired smooth pursuit eye movement. Lamotrigine produced only a possible slight increase in body sway. There were significant correlations between performance and saliva levels of phenytoin and diazepam. The tests used were suitable for monitoring central nervous system (CNS) effects of anticonvulsants and lamotrigine possibly could have a more favorable CNS side effect than phenytoin.

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L2 3 S L1 SSS SAM
L3 128 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 16:56:47 ON 04 APR 2007
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E US20050238724/PN,PRN,AN
L5 0 S E3/RN
L6 1 S E3

FILE 'REGISTRY' ENTERED AT 16:58:38 ON 04 APR 2007
L7 0 S L6

FILE 'HCAPLUS' ENTERED AT 17:00:04 ON 04 APR 2007
E LAMOTRIGINE+ALL/CT
S LAMOTRIGINE/CN

FILE 'REGISTRY' ENTERED AT 17:00:26 ON 04 APR 2007
L8 1 S LAMOTRIGINE/CN

FILE 'HCAPLUS' ENTERED AT 17:00:27 ON 04 APR 2007
L9 1265 S L8





L10 27 S "3,5-DIAMINO-6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE"

FILE 'REGISTRY' ENTERED AT 17:02:26 ON 04 APR 2007
L11 1 S 84057-84-1/RN

FILE 'HCAPLUS' ENTERED AT 17:02:48 ON 04 APR 2007
L12 1265 S L11
L13 111187 S L10 OR L12 AND PARTICLE OR GRANULE
L14 0 S L12 (N) PARTICLE
L15 0 S L12 (W) PARTICLE
L16 46 S L12 AND CNS

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=> s aronhime,j?/au or samburski,g?/au
           86 ARONHIME,J?/AU
            8 SAMBURSKI,G?/AU
L17        91 ARONHIME,J?/AU OR SAMBURSKI,G?/AU

=> s aronhime,j?/au and samburski,g?/au
           86 ARONHIME,J?/AU
            8 SAMBURSKI,G?/AU
L18         3 ARONHIME,J?/AU AND SAMBURSKI,G?/AU

=> d l18 1-3 ibib abs

L18  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:259910  HCAPLUS
DOCUMENT NUMBER:          146:281059
TITLE:                    Solid particulate tadalafil having a bimodal particle
                          size distribution
INVENTOR(S):              Aronhime, Judith; Samburski, Guy;
                          Ovadya, Yhoshoa
PATENT ASSIGNEE(S):       Teva Pharmaceutical Industries Ltd., Israel; Teva
                          Pharmaceuticals USA, Inc.
SOURCE:                   PCT Int. Appl., 19pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2007027612         A2    20070308    WO 2006-US33541         20060829
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
             KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
             MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
             RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                        US 2005-712589P     P  20050829
AB   Provided is a solid particulate tadalafil having a bimodal particle size
     distribution.  The solid particulate tadalafil is useful for the manufacture of
     a medicament for the treatment of sexual dysfunction.  Thus, 2 g of a
     solid particulate tadalafil having a bimodal particle size distribution
     were prepared by combining 0.38 g of large particle size tadalafil and 1.62
     g of small particle size tadalafil.  Calcn. of the amount of large particle
     size particulate tadalafil was presented.

L18  ANSWER 2 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2006:543943  HCAPLUS
DOCUMENT NUMBER:          145:45919
TITLE:                    Process for the preparation of ezetimibe polymorphic
                          crystalline forms
INVENTOR(S):              Aronhime, Judith; Koltai, Tamas;
                          Samburski, Guy; Lehrman, Ori; Izsak, Reuven
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PATENT ASSIGNEE(S):       Teva Pharmaceutical Industries Ltd., Israel; Teva
                          Pharmaceuticals Usa, Inc.
SOURCE:                   PCT Int. Appl., 54 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2006060808         A1    20060608    WO 2005-US44065         20051205
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX,
             MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
             SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
             VN, YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
     US 2006160785         A1    20060720    US 2005-295141          20051205
PRIORITY APPLN. INFO.:                        US 2004-632543P     P  20041203
                                              US 2005-649139P     P  20050203
                                              US 2005-668571P     P  20050406
                                              US 2005-687316P     P  20050606
                                              US 2005-712781P     P  20050830
                                              US 2005-717275P     P  20050914
AB   Processes are described for preparing polymorphic crystalline forms of
ezetimibe,
     such as ezetimibe Form A or Form B, for example, by precipitating ezetimibe
from
     selected solvents.  Some forms may be transformed into different forms at
     elevated temps., or under various humidity conditions, or by
     micronization.
REFERENCE COUNT:          8     THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18  ANSWER 3 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2003:875073  HCAPLUS
DOCUMENT NUMBER:          139:354488
TITLE:                    Pharmaceutical composition containing lamotrigine
                          particles of defined morphology
INVENTOR(S):              Aronhime, Judith; Samburski, Guy
PATENT ASSIGNEE(S):       Teva Pharmaceutical Industries Ltd., Israel; Teva
                          Pharmaceuticals USA, Inc.
SOURCE:                   PCT Int. Appl., 24 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2003090693         A2    20031106    WO 2003-US13002         20030423
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| WO 2003090693 | A3 | 20040108 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
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| EP 1496864 | A2 | 20050119 | EP 2003-728552 | | 20030423 |
| EP 1496864 | B1 | 20070321 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | | |
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AB The present invention provides a pharmaceutical composition comprising a plurality of lamotrigine particles having a sp. surface area of from about two to about three and a half meters per g. Pharmaceutical compns. falling within the surface area criteria for the lamotrigine particles include those having a particle diameter equal to or less than about 100 μm, preferably about 50 μm, and most preferably 10 μm. The pharmaceutical composition can be formulated into a wide variety of dosage forms for treatment of seizures.